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INFLAMMATION OF SEROUS SURFACES

HYDROGEN ION CONCENTRATION IN RELATION TO CELL TYPE

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With the demonstration that the polymorphonuclear (Müller [1a]; Müller and Jochmann [1b]; Opie [2]) and the clasmatocyte (Opie [2]) contain proteolytic enzymes active only within definite limits of hydrogen ion concentration of the medium, it was a question of time before the significance of these findings were investigated further in their relationship to the inflammatory process. Opie [3] in his earlier work on inflammation laid much of the groundwork for the investigations that followed. A definite cell sequence was repeatedly observed by many investigators after Borel [4] pointed out that the polymorphonuclear appears first and is followed later by the clasmatocyte. That the hydrogen ion concentration, the activity of phagocytic cells and the sequence of cells may bear a relationship appealed to some investigators. Fenn [5] demonstrated that under the conditions of his experiments the phagocytic activity of the leukocytes is seriously influenced by the concentration of hydrogen ions in the medium. Rohde [6] and Kempner and Paschel [7] found a tendency of the inflammatory exudate to assume an acid reaction. On the other hand, Rous [8] found that the interior of the cell with its enzymatic activity was not influenced by the hydrogen ion concentration of the external medium. Menkin [9] brought this rela-

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1. (*a*) Müller, F., quoted by Zinsser, H.: Infection and Resistance, New York, The Macmillan Company, p. 368. (*b*) Müller, F., and Jochmann, G.: München. med. Wchnschr. **53**:1393 and 1507, 1906.
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6. Rohde, C.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **40**:85, 1926.
7. Kempner, W., and Paschel, C.: Ztschr. f. klin. Med. **114**:439, 1930.
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tionship between cell sequence and hydrogen ion concentration to its apparent conclusion. He deduced from his experiments that the cytologic picture in inflammation is dependent on the hydrogen ion concentration of the exudate. An alkaline medium (with p_H about 7.3 to 7.4) is consistent with polymorphonuclear exudation, and an acid environment evokes the clasmatocyte. It must be pointed out that the colorimetric method of determining p_H was used by all the aforementioned investigators. Colorimetric methods under the conditions of those experiments are subject to considerable error. Some of the factors which may render the p_H determinations unreliable are the transfer of the inflammatory exudate with its rapid changes in gaseous content, the effect of the exudate proteins and temperature, the transfer of exudate to vessels, the addition of solutions and the error of subjective interpretations of color. The purpose of this work is to review the relationship of the hydrogen ion concentration of inflammatory exudates under the conditions of our experiments to the type of cell, employing a method of determining p_H presumably less subject to error than the colorimetric.

EXPERIMENTAL PROCEDURES

Peritoneal inflammation was produced in dogs and rats by the intraperitoneal introduction of bacterial cultures and leukocyte-stimulating substances. The p_H of the peritoneal exudate of the dogs and rats (anesthetized with ether or pentobarbital sodium) was determined with the Beckman electric potentiometer. The readings taken with the potentiometer were verified by frequent checks of buffered solution of known hydrogen ion concentration. Glass electrodes, connected to the meter by a cable, were introduced directly into the peritoneal cavity immediately after a small abdominal incision was made to allow their entrance. By employing this procedure, the effects of exposure to air and of change in temperature were minimized. Total and differential cell counts were made on the exudate immediately after the p_H was determined.

p_H readings were made of the peritoneal exudate within the peritoneal cavity, and then at five minute intervals exudate was removed and determinations were made promptly. It was found that the p_H of the exudate within the peritoneum differed from that of exudate outside the body. For example, the p_H of the exudate within the peritoneal cavity was 6.97, and that of the exudate outside the body at 25 C. was 8.11. There was a rapid change in the p_H after a few minutes. If p_H initially was 8.04, in five minutes it was 7.94, in ten minutes 7.82, and then it remained at that level for the next thirty minutes or the extent of the period in which the p_H readings were made.

p_H of Normal Animals.—The p_H of the peritoneal secretions of normal animals (rats and dogs) was determined prior to each set of experiments. In 20 normal albino rats it varied between 6.71 and 7.1; i. e., the reaction varied from acid to slightly alkaline. The readings in 5 normal dogs varied from 6.95 to 7.23 (table 1).

It was apparent that no individual animal, even of the same species, had a hydrogen ion concentration of the exudate of the normal peritoneal surface that

could be designated as a constant normal. Readings for the normal members of a given animal species had a variable range from an acid reaction to an alkaline one. Consequently, a determined p_H, to be considered abnormal, must be either below or above the range determined for the normal animal of that species.

p_H in Staphylococcic Infections.—A forty-eight hour broth culture of Staphylococcus aureus was injected intraperitoneally in 2 cc. volumes into 30 rats. The bacterial culture was suspended in a 1 per cent solution of tragacanth to insure a peritoneal infection and exudation.[10] At intervals of from five hours to seven days after the injection of the bacteria, from 2 to 3 rats of the series were anesthetized and the hydrogen ion concentration of the peritoneal exudate determined. Total white cell and differential counts were made and correlated with the p_H readings. The p_H of the staphylococcus culture prior to injection into the animals was 8.57. The readings of normal rats for this experiment varied between 6.82 and 7.1.

The readings obtained on the peritoneal exudate of the 30 infected rats over a period of seven days varied between 6.6 and 7.22. The extremes of these determinations represented either more acid or more alkaline reactions than those estab-

TABLE 1.—*The Hydrogen Ion Concentration of Peritoneal Secretion in Situ as Determined in Normal Animals with the Beckman Electric Potentiometer and Glass Electrodes*

Rat	p_H	Rat	p_H	Dog	p_H
1	6.71	11	6.87	1	6.95
2	6.71	12	6.98	2	6.96
3	6.71	13	7.00	3	7.04
4	6.75	14	7.00	4	7.20
5	6.77	15	7.04	5	7.23
6	6.77	16	7.07		
7	6.80	17	7.07		
8	6.82	18	7.10		
9	6.82	19	7.10		
10	6.85	20	7.10		

lished for the entire normal group of animals. However, correlation of the p_H, the differential and the total cell count and the number of degenerated cells and bacteria in the peritoneal smears failed to establish any obvious relationship between the hydrogen ion concentration and the cell type or the number of degenerated cells or the relative number of free or phagocytosed bacteria (table 2). For example, a p_H of 6.6 was associated with a polymorphonuclear percentage of 91 and a clasmatocyte percentage of 8 in a total count of 16,500 per cubic millimeter. On the other hand, a peritoneal exudate with 58 per cent polymorphonuclears and 32 per cent clasmatocytes in a total count of 14,500 per cubic millimeter showed a hydrogen ion concentration of 7.10. The other p_H determinations on the rats in this series of experiments (with staphylococcic infection) showed either an acid or an alkaline reaction irrespective of a low or a high percentage of polymorphonuclears or clasmatocytes. If any factor resident in the environment of the animal is responsible for the variations in p_H, that factor is apparently not included in those considered in this experiment.

Each of 5 dogs was given intraperitoneally 10 cc. of a forty-eight hour culture of Staph. aureus (p_H 8.57). At intervals of between one and seven days an animal was anesthetized and the hydrogen ion concentration and the total and differential white cell counts of the peritoneal exudate were determined. The p_H of the exudate varied between 6.67 and 7.12. The polymorphonuclear percentage was

10. Steinberg, B.: Am. J. Clin. Path. **6**:253, 1936.

in no instance less than 92. It is obvious that no relationship could be established in this experiment between cell type and hydrogen ion concentration (table 2). Although the polymorphonuclears in one animal constituted 96 per cent of 288,000 cells per cubic millimeter, the p_H was distinctly on the acid side (6.84).

Ten rats were given subcutaneous injections of heat-killed cultures of Staph. aureus over a period of two weeks. Each of 5 other rats received three intraperitoneal injections of a similar staphylococcus culture. In the third week, each of the 15 vaccinated rats was given 2 cc. of a living forty-eight hour broth culture of Staph. aureus intraperitoneally, At intervals of from one hour to five days, a rat was anesthetized, and the p_H of the peritoneal exudate was determined and complete and differential white cell counts were made. The p_H varied from 6.7 to 7.10 with greater or lesser percentages of polymorphonuclears either on the acid or on the alkaline side. There was no apparent relationship between the cell type

TABLE 2.—*The Relationship of the Cell Type to the p_H of Peritoneal Exudate In a Staphylococcic Infection of the Peritoneum (p_H of Staphylococcic Culture 8.57)*

Rats*					Dogs*				
	Percentage of					Percentage of			
p_H	Polymorphonuclears	Clasmatocytes	Other Cells	Total White Cell Count	p_H	Polymorphonuclears	Clasmatocytes	Other Cells	Total White Cell Count
	Acid Side					Acid Side			
6.6	91	8	1	16,500	6.67	98	0	2	111,750
6.87	92	0	8	4,600	6.84	96	4	0	288,000
6.89	71	12	17	24,250	6.91	98	0	2	45,000
6.90	69	20	11	16,500					
6.98	52	34	14	11,750					
	Alkaline Side					Alkaline Side			
7.02	31	33	36	45,500	7.08	95	4	0	57,750
7.03	84	14	2	36,000	7.12	92	1	8	34,500
7.10	58	32	10	14,500					
7.12	78	12	10	43,000					
7.22	82	11	7	8,250					

* For the sake of brevity, the table is condensed to include only representative results obtained on the rats and dogs. Repetitious experiments are omitted.

and the p_H either in the subcutaneously or in the intraperitoneally vaccinated animals which received subsequently a staphylococcic infection.

p_H in Pneumococcic Infections.—A forty-eight hour culture of a virulent pneumococcus, type I, was mixed with an equal volume of a homologous antiserum, and 2 cc. amounts of the mixture were injected intraperitoneally into 30 albino rats. From 1 to 5 rats were anesthetized at intervals of between five hours and seven days, and the p_H of the peritoneal exudate and the total white cell and the differential count were recorded. The p_H of the culture serum mixture injected was 4.90. In the fifth hour after the injection, the p_H of the exudate was 6.95 with 85 per cent polymorphonuclears, 1 per cent clasmatocytes and 14 per cent lymphocytes in a total count of 8,100 per cubic millimeter. In twenty-four hours, the p_H was 6.91 with 58 per cent polymorphonuclears and 37 per cent clasmatocytes, the total count being 16,250 per cubic millimeter. At the sixty-sixth hour, 5 rats were anesthetized, and the p_H was found to vary between 6.8 (19 per cent polymorphonuclears and 69 per cent clasmatocytes) and 7.08 (22 per cent polymorphonuclears and 55 per cent clasmatocytes). On the seventh day, 2 rats were anesthetized, and the exudate of one was determined to have a p_H of 6.76 with

89 per cent polymorphonuclears and 10 per cent clasmatocytes in a total count of 32,500 per cubic millimeter, while the exudate of the other had a p_H of 6.90 with 1 per cent polymorphonuclears and 98 per cent clasmatocytes.

Each of 3 dogs was given an intraperitoneal injection of 10 cc. of a forty-eight hour broth culture of a virulent pneumococcus, type I, suspended in a 1 per cent solution of tragacanth and mixed with 10,000 units of a homologous antiserum. A dog was anesthetized each day for three days, and the p_H of the peritoneal exudate was determined and total white cell and differential counts were made. The peritoneal cavity of one dog contained 201,000 white cells per cubic millimeter with polymorphonuclears comprising 93 per cent of the cells. The p_H was 6.69. Another dog had 43,250 cells per cubic millimeter with 80 per cent polymorphonuclears and 14 per cent clasmatocytes and a p_H of 7. No apparent relationship between the cell type and the p_H of the exudate could be established in these experiments either on the rats or on the dogs with pneumococcic infections.

Peritoneal Inflammation with Bacillus Diphtheriae and with Botulinus Toxin.—Ten rats were treated by injection of a 1 per cent tragacanth suspension of a

TABLE 3.—*The Relationship of the Cell Type to the p_H of Peritoneal Exudate in Pneumococcic Infection of the Peritoneum (p_H of Pneumococcus Culture 4.90)**

Rats					Dogs				
	Percentage of					Percentage of			
p_H	Polymorphonuclears	Clasmatocytes	Other Cells	Total White Cell Count	p_H	Polymorphonuclears	Clasmatocytes	Other Cells	Total White Cell Count
6.93	49	44	7	16,000	6.89	93	3	4	201,000
6.95	85	1	14	8,100	6.76	94	6	..	22,400
6.95	78	20	2	4,250	7.00	80	14	6	43,250
6.97	81	10	9	23,000					
6.80	19	69	11	57,200					
7.05	77	19	4	9,200					
7.08	22	55	23	16,000					
7.08	34	50	16	24,000					

* The table is condensed for the sake of brevity, only representative results being given.

twenty-four hour blood agar culture of B. diphtheriae. Each rat received intraperitoneally 5 cc., containing one fifth of an average size culture slant. The p_H of the tragacanth–bacterial mixture was 5.36. One or two rats were anesthetized at intervals of between twelve hours and five days. The p_H of the peritoneal exudate was determined and total white cell and differential counts were made. In twelve hours, the p_H was 7.10 with 88 per cent polymorphonuclears, 8 per cent clasmatocytes and 4 per cent eosinophils in a total count of 14,500 per cubic millimeter. In forty-eight hours, the p_H was 7.14 with 48 per cent polymorphonuclears, 48 per cent clasmatocytes and 4 per cent lymphocytes in a total count of 48,000 per cubic millimeter. On the fifth day, the p_H was 6.94 with 29 per cent polymorphonuclears and 39 per cent clasmatocytes, eosinophils and lymphocytes making up the rest of the 32 per cent. No correlation was apparent in this experiment (with B. diphtheriae) between the cell type and the hydrogen ion concentration of the peritoneal exudate.

Each of 4 dogs was given intraperitoneally one slant of a twenty-four hour culture of B. diphtheriae grown on blood agar and suspended in 20 cc. of a 1 per cent solution of tragacanth. Three hours later, each animal received subcutaneously 20,000 units of diphtheria antitoxin. The animals were anesthetized at one, two, three, five and seven day intervals, and the p_H of the exudate was deter-

mined and total and differential cell counts were made. On the second day, the p_H was 7.19 with 100 per cent polymorphonuclears in a total cell count of 100,000 per cubic millimeter. In five days, the p_H was 7.13 with 94 per cent polymorphonuclears and 6 per cent clasmatocytes (total count, 55,250 per cubic millimeter). On the seventh day, the p_H was 7.03 with 91 per cent polymorphonuclears, 7 per cent clasmatocytes and 2 per cent lymphocytes and a total count of 146,000 per cubic millimeter. In this experiment (with passive immunity) there was a consistently alkaline exudate associataed with an invariably high polymorphonuclear content.

Each of 10 rats received intraperitoneally 0.1 cc. of botulinus toxin (minimal lethal dose, 0.0008 cc.) in 1.9 cc. of a 1 per cent solution of tragacanth. At intervals of between twelve hours and five days, one or two rats were anesthetized, and the p_H of the exudate was determined and total and differential cell counts were made. Four of the rats died before the work could be done. In twelve hours, one animal had an exudate with 500 cells per cubic millimeter, which was predominantly polymorphonuclear, and a p_H of 7.15. On the second day, the p_H was 7.23 with 63 per cent polymorphonuclears, 30 per cent clasmatocytes and 7 per cent lymphocytes (total count of 16,500 per cubic millimeter). On the fifth day, the p_H was 7.04 with 96 per cent clasmatocytes and 4 per cent polymorphonuclears (total count of 8,500 per cubic millimeter).

There is apparently no obvious relationship in these experiments (with botulinus toxin) between the cell type and the hydrogen ion concentration of the peritoneal exudate.

Buffer Action of the Peritoneum.—An attempt was made to evaluate the results so far obtained in the light of the possible buffer action of the peritoneum. One per cent lactic acid (p_H 2.33) was injected intraperitoneally in 5 cc. quantities into 14 rats. At intervals of several minutes, 2 rats were anesthetized, and the p_H of the peritoneal fluid determined. The p_H of the peritoneal fluid of 6 normal rats showed a variation between 6.85 and 7.20. If 6.85 is accepted as the lowest normal reading on the acid side, the peritoneum showed a return to a normal hydrogen ion concentration in from fifteen to thirty minutes after the introduction of the lactic acid. The change in the p_H began to take place within a minute, and the subsequent change progressed rapidly, reaching a p_H of 6.73 in fifteen minutes (table 4).

A 1 per cent solution of sodium bicarbonate with a p_H of 8.31 was injected intraperitoneally in 5 cc. quantities into 12 rats. At intervals of several minutes, 2 rats were anesthetized, and the p_H of the peritoneal fluid determined. If 7.20 is accepted as the highest alkaline reading of a normal rat, the return to normal was apparent in some of the animals within from thirty to forty-five minutes (table 4). These experiments indicate that the peritoneum is capable of buffering rather rapidly either acid or alkaline solutions. The buffering action is more rapid with acid solutions than with alkaline.

In order to determine the rapidity of the buffering action of the peritoneum in the presence of an acid bacterial culture, a forty-eight hour dextrose broth culture of a pneumococcus was injected in 5 cc. quantities into 20 rats. The p_H of the culture was 4.93. At intervals of several minutes, one or two rats were anesthetized, and the p_H of the peritoneal exudate determined. To establish the normal p_H for this experiment, the p_H of 5 normal rats was determined. The p_H for the normal animals varied between 6.90 and 7.02. In twenty-four minutes, the rats showed a return of the p_H to normal limits. The buffering action proceeded most rapidly in the first ten minutes (table 5).

To evaluate the possible buffering activity of an inflamed peritoneum, each of 15 rats was given three intraperitoneal injections of 5 cc. of a mixture of tragacanth, formaldehydized colon bacilli and aleuronat (an albuminoid substance and lecithin) [10] over a period of nine days. Three days after the last injection, each of 11 rats received intraperitoneally 5 cc. of a viable forty-eight hour dextrose broth culture of a pneumococcus, type I (p_H 4.80). To establish the normal limits of the hydrogen

TABLE 4.—*The Buffering Action of the Peritoneum Following Intraperitoneal Injection of Either Lactic Acid or Sodium Bicarbonate, As Determined in Rats* *

Lactic Acid (p_H 2.33 at 23 C.)		Sodium Bicarbonate (p_H 8.31 at 23 C.)	
Time After Injection, Minutes	p_H of 2 Rats at Specified Intervals	Time After Injection, Minutes	p_H of 2 Rats at Specified Intervals
1	3.46; 3.40	6	7.67; 7.62
6	4.50; 4.18	12	7.63; 7.47
10	4.88; 4.90	19	7.35; 7.23
15	6.57; 6.73	30	7.40; 7.30
30	7.10; 7.10	45	722.; 7.20
45	7.12; 7.05	60	7.32; 7.01
60	7.15; 7.15		

* p_H was determined for 6 normal rats immediately before the experiment and was as follows: 6.85; 6.98; 7.00; 7.07; 7.10; 7.20.

TABLE 5.—*The Buffering Action of the Normal and of the Inflamed Peritoneum Following Injection of Acid Bacterial Cultures* *

Pneumococcic Culture (p_H 4.98 at 23 C.) Injected into Normal Peritoneum		Pneumococcic Culture (p_H 4.80 at 23 C.) Injected into Inflamed Peritoneum				
					Percentage of	
Time After Injection, Min.	p_H	Time, Min.	p_H	Total White Cell Count	Polymorphonuclears	Clasmatocytes
2	5.83	Before injection of pneumococcic culture	6.98	80,000	46	53
4	6.07; 6.10		7.20	102,000	91	9
5	6.19		7.05	52,000	76	17
8	6.40		7.08	40,500	52	6
11	6.63	After injection	4	6.86	27,000	75
13	6.73		5	7.00	7,500	70
15	6.72		7	6.82	12,500	87
19	6.89		12	6.94	30,500	82
24	6.79; 6.95		20	6.96	34,000	84
28	6.97		30	6.97	19,000	87
30	6.96		45	7.15	4,000	82
32	7.08			7.07	36,000	91
38	7.00		90	7.18	91,500	97
45	6.84			7.15	5,750	97
60	7.06; 7.11		120	7.11	51,000	95
120	7.15; 7.18					

* p_H was determined for 5 normal rats immediately before the experiment and was as follows: 6.90; 6.98; 6.96; 7.02; 7.02.

ion concentration of the peritoneal exudate in the rats given the leukocyte-evoking preparation, the p_H of the peritoneal exudate of the 4 rats not infected with pneumococci was determined (6.98 to 7.20). Also, total and differential white cell counts were made on the exudate of these rats. Every several minutes, an infected animal was anesthetized, and the p_H of the peritoneal exudate was determined and total and differential white cell counts were made. In five minutes, the p_H returned to the normal level. The rapidity of the return to a normal level may be accounted for as due to the dilution of the bacterial culture by the exudate (table 5).

COMMENT

The hydrogen ion concentration of normal peritoneal secretion was determined on albino rats and dogs with the Beckman electric potentiometer, connected by a cable to glass electrodes. The glass electrodes were introduced directly into the peritoneal cavity and the p_H reading taken. This method obviated many of the errors incident to other methods. Inflammation was induced with various bacteria (pneumococci with an acid medium, staphylococci with an alkaline medium) and a bacterial toxin, and the p_H of the exudate was determined together with the cellular picture. Alkaline and acid solutions were introduced intraperitoneally, and the buffer action was determined in normal and inflamed peritoneums.

There was a variation in the p_H of the normal peritoneum in members of the same animal species and in members of different species. This individual variation was less in the presence of an inflammatory process. After injection of an acid or an alkaline solution into the peritoneal cavity with either normal or an inflamed peritoneum, there occurred a reduction of the p_H to a normal reading within thirty minutes. The hydrogen ion concentration showed no relationship to the type of cell predominant in the exudate, to the type of bacterium or toxin used or to the duration of the inflammatory process.

CONCLUSIONS

There is no apparent relationship between the cell sequence and the hydrogen ion concentration of the inflammatory exudate produced under the conditions of our experiments.

The body tends to bring to its usual concentration of hydrogen ions the concentration of hydrogen ions of injected fluids whether these are more alkaline or more acid. This occurs whether the tissues are normal or subject to an inflammatory process of short or long duration.

There is a variability of the p_H of the normal peritoneum. This variability may be inherent in the peritoneum and due to the individual differences in the members of the same animal species or may be dependent on the technical equipment and methods. The range of variability is, however, smaller in the animal with an inflammatory process in the peritoneum than in the normal animal.

INFLAMMATION OF SEROUS SURFACES

TRANSFER OF LIVING LEUKOCYTES AND THE EFFECT ON ACUTE INFECTIOUS STATES

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That inflammation is essentially a defense mechanism is universally accepted. Present understanding, however, of the function of the various inflammatory elements in relation to defense is incomplete. Of these elements, the cell and its constituent structures are probably the most important and intriguing. For many years, the polymorphonuclear was accepted as the principal factor in defense against acute infections. But lately, even this apparently elementary concept is being challenged. Consequently, it is not remiss to reexamine these problems, perhaps from an aspect not hitherto investigated.

This work concerns itself with the transfer of living leukocytes, principally polymorphonuclears, from animal to animal of the same and of different species and with the functional significance of such transferred cells in the presence of acute infectious states of the serous membrane. Previous workers were concerned essentially with the action on bacteria of possible bactericidal substances contained within the leukocyte. Schattenfroh [1] found such bactericidal substances in saline extracts of leukocytes. Pettersson,[2] Opie,[3] Zinsser,[4] and Hiss [5] extended and amplified knowledge of the character of these bacterial extracts in relation to various micro-organisms and animal hosts. These workers, however, were not concerned with the leukocyte as an intact cell in its relation to bacterial defense.

Linton,[6] while working with Gay on the problem of local immunity, transferred irritated omentum of rabbits and of guinea pigs into the peritoneal cavities of rabbits. Subsequent intrapleural infection of these rabbits with Streptococcus haemolyticus resulted in the survival of 70

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per cent of the animals. Linton assumed that the survival was due to the presence of a large number of clasmatocytes in the irritated omentum and the passage of these cells through the diaphragm.

TRANSFER OF LEUKOCYTES FROM ANIMAL TO ANIMAL OF THE SAME SPECIES

Leukocytic exudation was induced either in the peritoneal or in the pleural cavities of dogs by introducing 50 cc. of the leukocyte-evoking preparation previously described.[7] The exudate was withdrawn at intervals varying from three hours to fourteen days. Not all the animals responded equally either in volume of exudate or in number of leukocytes. In some of the dogs, as much as 1,000 cc. containing 350,000 cells per cubic millimeter was secured; in other animals, scarcely 20 cc., with a cell count, however, of not less than 90,000. It was observed that splenectomized animals (from another experiment) uniformly produced greater volumes of exudate as well as greater numbers of cells within two or three months after splenectomy. Smears of all the exudates used in the experiments revealed that the polymorphonuclears constituted from 86 to 98 per cent of the total number of cells, with lymphocytes, monocytes and clasmatocytes forming the remaining number.

As a criterion of the functional activity of the leukocytes, the following procedure was employed: A peritoneal infection, uniformly fatal, was induced in dogs. At varying intervals after the induction of the lesions, varying numbers of leukocytes of varying age in vitro or in vivo were introduced intraperitoneally. If the animals survived, it constituted proof of functional activity on the part of the introduced leukocytes. Death was accepted as evidence of a functional failure.

The fatal peritoneal infection was induced by introducing into the peritoneal cavity with a needle and a syringe 8 billion virulent colon bacilli (a stock culture, no. 300) grown for twenty-four hours on veal agar slants and suspended in 40 cc. of a 2 per cent solution of tragacanth U. S. P. The average life of the animals was from six to sixteen hours.

Since the cell exudate obtained with the leukocyte-evoking substance[7] was composed of other elements than leukocytes, experiments were designed to determine the functional activity of the constituent factors. The pleural and the peritoneal exudate were divided into equal parts. One part was centrifuged and the supernatant serum preserved. The sedimented peritoneal cells were washed five times, shaken continuously with glass beads until broken up, and resuspended in normal physiologic solution of sodium chloride.

Peritoneal infection was induced in 38 dogs by the method described, and then the dogs were divided into five groups. One group, 9 animals, was given an intraperitoneal injection of pooled leukocytic peritoneal exudate, each dog receiving 4 billion leukocytes, from fifteen to sixty minutes after infection. The second group, 5 dogs, was given an injection of broken-up cells suspended in salt solution, equivalent to 4 billion leukocytes for each animal. A third group, 5 dogs, was given an injection of the supernatant peritoneal serum, and the fourth group, also 5 dogs, an injection of the supernatant pleural serum, obtained after centrifuging the whole exudate. Each of the animals of the third and fourth series received 200 cc., which was equivalent in volume to the whole exudate for each dog in the first group. A fifth group, 14 dogs, with a peritoneal infection were left as controls.

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7. Steinberg, B.: Am. J. Clin. Path. **6**:253, 1936.

The 14 controls died in from six to sixteen hours. Of the 9 dogs given the injection of the whole leukocytic exudate following infection, 8 survived and 1 died in three days. Of the 5 animals given the injection of washed and broken-up cells, all died in from eight to twelve hours. Each of the 5 dogs given the supernatant pleural serum died in from eight to twenty-four hours. One of the 5 animals treated with the supernatant peritoneal serum survived; the other 4 died in from sixteen to twenty-four hours (table 1).

The course of the defensive mechanism between the infectious process and the injected leukocytic exudate and its component parts was followed by studies of peritoneal fluid obtained by puncture at intervals of fifteen minutes for the first hour and at hourly intervals for several days, on all the dogs receiving injections of the various materials. The studies consisted in making total and differential cell counts, also bacterial counts (by transplanting measured volumes of peritoneal fluid on Petri dishes with agar) and in determining the degrees of phagocytosis and the numbers of free micro-organisms.

TABLE 1.—*Functional Outcome in Animals with a Peritoneal Infection and Subsequent Injection of Living Leukocytes in Exudate from Animals of the Same Species*

Dogs	Character of Injected Material	Animals That Died	Duration of Life, Hr.	Percentage of Survival
14	None	14	6-16	0
9	Whole leukocytic exudate with 4 billion cells for each dog	1	72	88
5	Broken-up cells suspended in salt solution (a saline extract) equivalent to 4 billion cells for each dog	5	8-12	0
5	200 cc. of the supernatant fluid from centrifuged peritoneal exudate, equivalent in volume to the whole exudate used for each dog in the first group	4	16-24	20
5	200 cc. of the supernatant fluid from centrifuged pleural exudate	5	8-24	0

The total and differential cell counts and bacterial counts were done on the 14 control animals of this experiment and on approximately 200 other dogs in former experiments.[8] The results given here are those obtained on one dog representing the usual average response of a control animal to a constant type of peritoneal infection produced by the method described. In the first hour, the total white cell count was 2,400, with 94 per cent polymorphonuclears and 6 per cent lymphocytes and desquamated epithelial cells. In the second hour there were 12,500 cells; in the third hour 28,000, with approximately that level for the next three hours, followed by a sudden drop at each succeeding hour up to death, at which time the total count was 13,400. The polymorphonuclears averaged from 92 to 100 per cent. There was marked phagocytosis, but there were also numerous free bacteria, which increased in number during succeeding hours. The total bacterial count (free and phagocytosed bacteria) showed at first a marked decrease

8. Steinberg, B., and Snyder, D. A.: Arch. Path. **8**:419, 1929. Steinberg, B.: Arch. Surg. **24**:308, 1932; Am. J. Clin. Path. **2**:187, 1932. Steinberg, B., and Goldblatt, H.: Surg., Gynec. & Obst. **57**:15, 1933.

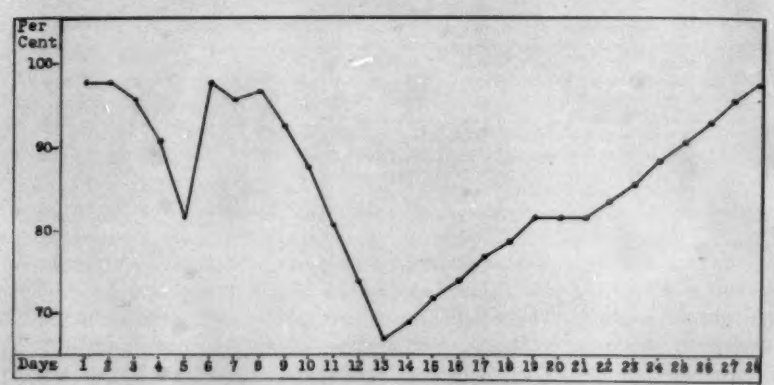
and then a subsequent increase (table 2). It was apparent that the invading colon bacilli were being phagocytosed, but there was an insufficient number of leukocytes for the bacteria present.

In the 9 dogs treated with whole exudate, the total cell count fifteen minutes after the injection of the exudate averaged 84,500, with 97 per cent of the cells polymorphonuclears. By the end of the first hour the count was 56,000, with 97

TABLE 2.—*Relative Bacterial Counts per Cubic Centimeter of Peritoneal Exudate in a Control Dog with Peritoneal Infection Only and Another Dog with Peritoneal Infection Plus Treatment with Leukocytic Exudate*

Hours	Control Dog with Peritoneal Infection	Dog with Peritoneal Infection, Treated by Injection of Leukocytic Exudate
1	27,360,000	58,000
2	33,000,000	27,500
3	14,000,000	40,000
4	6,740,000	31,000*
5	88,000	37,500
6	240,000	21,450
7	560,000	11,500
8	14,000,000	19,000
9	10,300,000	27,500
10	4,160,000 Died†	6,500

* From the fourth hour no free bacteria were seen in stained smears.
† Free bacteria were seen in large numbers every hour.



Percentage of polymorphonuclears in relation to the total number of leukocytes in the peritoneal exudate of a dog with peritoneal infection and transferred leukocytes from another animal of the same species. The chart is a representative one from among the charts of a large number of animals studied.

per cent polymorphonuclears; in the second hour, 91,000, with 97 per cent polymorphonuclears. In the succeeding hours, the cell count varied between 68,000 and 98,000, rising at the end of the first day to 240,000, with a polymorphonuclear percentage of 95 or more. In the following four hours there was a steady decline in the polymorphonuclears to the lowest level of 67 per cent. In the next sixteen hours, the polymorphonuclears slowly increased in percentage to 97 (chart 1).

Free bacteria disappeared in the first two or three hours as contrasted with an ever increasing number of free bacteria in the control dogs. Bacterial counts

(which included free and phagocytosed bacteria) showed a marked drop in the first hour with a subsequent more gradual decrease (table 2). The bacterial cultures, however, remained positive for a period of from seven to ten days.

Phagocytosis of the invading bacteria was almost complete in an hour. The number of leukocytes with phagocytosed bacteria were relatively few (from 10 to 16 per cent), but each leukocyte contained from 17 to 50 bacteria. The engorgement of the leukocytes with the bacteria and the subsequent cell disintegration, bacterial release and multiplication may account for the variation in the bacterial counts and the variation in the presence of free organisms in the smears.

INTERPRETATIONS OF THE EXPERIMENTS

Survival of the animals (8 of 9) with an acute peritoneal infection and leukocytic exudate and the death of animals treated with dissociated components of the exudate (bacterial extract, supernatant serum) indicate that the cellular element (the polymorphonuclear) was responsible for the survival. It is further apparent that living leukocytes removed from one animal and injected into another animal of the same species overcome an otherwise lethal infection as produced in these experiments. From the studies of the peritoneal struggle, it may be deduced that phagocytosis was the process responsible for survival of the animals. It may be further assumed that the phagocytic function is preserved in transferred leukocytes and that phagocytosis is rapid and hence that survival or death is determined early in the infection. That phagocytosis was the principal defense reaction in these experiments is substantiated by the high total cell counts, the absence of free bacteria and the marked phagocytic activity of the cells. In contrast, the control animals had low cell counts and evinced a failure of phagocytosis and the presence of many free bacteria.

TRANSFER OF LEUKOCYTES FROM ANIMAL TO ANIMAL OF DIFFERENT SPECIES

Peritoneal infection was induced in 22 rabbits by injecting intraperitoneally into each 2 billion virulent colon bacilli suspended in 15 cc. of a 2 per cent solution of tragacanth U. S. P. in physiologic solution of sodium chloride. The rabbits were divided into two groups. One group, 12 animals, received at varying intervals, from fifteen minutes to one hour after the infection, pooled peritoneal leukocytic exudate obtained from dogs. Each rabbit received 4 billion leukocytes. The other group, 10 rabbits with peritoneal infection, were used as controls and were not given leukocytic exudate. Of the 12 rabbits with infection and leukocytes, 8 survived. All of the 10 control rabbits died in from six to sixteen hours. Those of the rabbits in the group of 12 treated with leukocytic exudate one hour after peritoneal infection died, although the duration of life was prolonged (table 3). Another group, 4 rabbits, was given dog leukocytic exudate only. All the animals survived.

Studies of the peritoneal fluid removed from the treated rabbits showed a picture similar in principle to that observed in the treated dogs. There was rapid phagocytosis of the bacteria, and in ninety minutes there were no free micro-organisms.

The phagocytosis was evidently accomplished by the dog leukocytes. The rabbit leukocytes, which began to appear within one hour, could be readily differentiated because of the more pronounced eosinophilia of the cytoplasmic granules of the polymorphonuclears.

FACTORS INFLUENCING THE PHAGOCYTIC ACTIVITY OF TRANSFERRED LEUKOCYTES

In order to determine the influence of some of the factors acting on the phagocytic activity of transferred leukocytes, one of the factors was varied and the others

TABLE 3.—*Functional Capacity of Living Leukocytes That Were Transferred from One Animal (Dog) to Another Animal of a Different Species (Rabbit) with a Preexisting Peritoneal Infection*

Rabbits	Dog Leukocytes Administered	Time Between Infection and Administration of Dog Leukocytes, Min.	Rabbits That Died	Duration of Life, Hr.	Percentage of Survival
10 infected controls	0	..	10	6-12	0
4 noninfected controls	4 billion	..	..	.....	100
6	4 billion	15	2	12-72	66
4	4 billion	45	0	.....	100
2	4 billion	60	2	72	0

TABLE 4.—*Factors Influencing the Phagocytic Activity of Living Transferred Leukocytes*

Dogs	Variable Factor	Dogs That Died	Percentage of Survival
	Age of leukocytes outside of animal body		
9*	15 min. to 2 hr.	1	88
6	3 hr. or more	6	0
	Age of leukocytes within the peritoneal cavity		
5	4 hr.	1	80
13	12 hr. to 12 days	0	100
	Duration of the peritoneal infection before the introduction of leukocytes		
9*	15 min. to 1 hr.	1	88
4	2 hr.	4	0
2	3 hr.	2	0

* This is the same group as the group of 9 listed in table 1.

were allowed to remain constant. Peritoneal infection was induced in 15 dogs. Forty-five minutes later, pooled peritoneal leukocytes from dogs were injected in 4 billion quantities into these animals. The variable was the age of the leukocytes after their removal from the body of the animal. The age of the leukocytes varied from fifteen minutes to four hours. The results obtained divided the 15 animals into two groups. One group, 9 dogs, with injected leukocytes two hours or less in age, showed a survival of 88 per cent. The other group, 6 dogs, with leukocytes three hours or older, did not show survival of any of the animals. No apparent effect could be observed in varying the age of the leukocytes within the peritoneal cavity from four hours to twelve days before their removal and reinjection into other dogs with a preexisting infection (table 4). The polymorphonuclear percentage of the leukocytes varied between 98 at the fourth hour and 88 on the twelfth day.

The duration of the peritoneal infection was then varied, with the number of injected leukocytes remaining at a constant of 4 billions, their age outside the body at one hour and their age within the body at from one to four days. Since the infectious state produced under the conditions of these experiments was apparently severe, resulting in death in from six to sixteen hours, comparatively short intervals between the onset of infection and the injection of leukocytes were chosen. Of 9 animals with a peritoneal infection of up to one hour's duration, 8 survived. Of 6 animals with infections of two and three hours' duration, none survived.

Studies of the peritoneal fluid following the introduction of the leukocytes showed lack of bacterial phagocytosis by the leukocytes kept outside the body for over two hours. The leukocytes, however, were apparently alive, as interpreted by the appearance of the stained cells and the preservation of motility. In the animals with a peritoneal infection of two and three hours' duration, the phagocytosis was moderate. Instead of from 17 to 50 micro-organisms in a leukocyte, there were only from 2 to 12 in each cell. There were also numerous free bacteria. It is felt, however, that the failure of complete phagocytosis may not be the only cause of the death of these animals. Other experiments [9] indicate that there is an additional factor in the action of the secreted soluble toxic substances on the cardiovascular system.

SUMMARY

Polymorphonuclear leukocytes produced in the peritoneal or the pleural cavity of one animal (dog) may be transferred to the peritoneal cavity of another animal of the same species or of another species (rabbit) with preservation of the phagocytic function. The phagocytic function of transferred leukocytes is capable of preventing death from an otherwise fatal peritoneal infection as produced in these experiments. There are several factors which modify the outcome of the phagocytic function of transferred leukocytes. The length of time that untreated leukocytes have been kept outside the animal body and the duration of the infectious state are two of the investigated factors which interfere with a favorable outcome.

Constituents other than the intact polymorphonuclear cells in the exudate (serum and leukocytic extracts) play little or no part in the preservation of life in these experiments.

The polymorphonuclear leukocyte may be apparently alive and yet not capable of performing the function of phagocytosis under the conditions of these experiments.

9. Steinberg, B., and Kobacker, J. L.: J. Lab. & Clin. Med. **20**:1180, 1935.

INFLAMMATION OF SEROUS SURFACES

FACTORS MODIFYING TYPES OF CELL RESPONSE

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Experimental inflammation was first studied by Cohnheim,[1] who in 1867 demonstrated the migration of leukocytes from the blood stream to the tissues involved in inflammatory process. Borrel,[2] Durham[3] and others observed a definite cell sequence, with polymorphonuclears appearing first, followed later by clasmatocytes (macrophages). Metchnikoff[4] considered phagocytosis as the primary purpose of the inflammatory process, with the polymorphonuclear as the principal phagocytic cell and the clasmatocyte as a scavenger clearing up the débris of the struggle. The significance of the cell sequence as interpreted by Metchnikoff was soon questioned by Simon[5] and by Buxton and Torrey[6] who denied the importance of the polymorphonuclear in removing bacteria from the inflammatory field. Bordet,[7] Noetzel[8] and Wallgren,[9] as well as the aforementioned authors, indicated that the clasmatocytes possess a more important function in infection than that of scavenger cells. Gay and Morrison[10] departed still further from Metchnikoff's concept by interpreting their experiments to indicate that the presence of an excessive number of polymorphonuclears exerts a deleterious effect on recovery from infection. These investigators advanced the clasmatocyte as the cell essentially responsible for phagocytosis and enhanced resistance. Nakahara,[11] Ledingham[12] and Freedlander and

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1. Cohnheim, J.: Virchows Arch. f. path. Anat. **40**:1, 1867.
2. Borrel, A.: Ann. Inst. Pasteur **7**:593, 1897.
3. Durham, H. E.: J. Path. & Bact. **4**:338, 1897.
4. Metchnikoff, E.: Leçons sur la pathologie comparée de l'inflammation, Paris, G. Masson, 1892; L'immunité dans les maladie infectieuses, Paris, Masson & Cie, 1901.
5. Simon, F. B.: Centralbl. f. Bakt. (Abt. 1) **29**:113, 1901.
6. Buxton, B. H., and Torrey, J. C.: J. M. Research **15**:73, 1906.
7. Bordet, J.: Ann. Inst. Pasteur **11**:177, 1897.
8. Noetzel, W.: Arch. f. klin. Chir. **57**:311, 1898.
9. Wallgren, A.: Beitr. z. path. Anat. u. z. allg. Path. **25**:206, 1899.
10. Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**:338, 1923.
11. Nakahara, W.: J. Exper. Med. **42**:201, 1925.
12. Ledingham, J. C. G.: Brit. J. Exper. Path. **8**:12, 1927.

Toomey [13] observed phagocytosis by clasmatocytes and directly or by implication substantiated the interpretations of Gay and his associates. The ultimate negation of phagocytosis as a consistently universal defense reaction in inflammation was offered by Goodpasture and Anderson.[14] They interpreted their experiments to indicate that in many instances of bacterial invasion, both the clasmatocyte and the polymorphonuclear by their phagocytic activity do not retard but actually promote infection by favoring bacterial growth and invasion. The summation of the work on the defensive mechanism of inflammation appears to have reverted the subject to the pre-Metchnikoff era. These investigations, however, served the purpose of emphasizing the number and the complexity of the factors inherent in the problem. Since many of the workers employed animals and bacteria of different types and tissues of different types and sites, this investigation was undertaken to evaluate the effect of such variations on the final experimental results.

VARIATION OF ANIMAL SPECIES AND BACTERIAL TYPES IN THE PRODUCTION OF INFLAMMATION OF THE PERITONEAL SEROSA

In the following experiments the animal species used for the production of an inflammatory process were albino rats, New Zealand rabbits and mongrel dogs. The micro-organisms employed in inducing inflammation were: Staphylococcus aureus; Diplococcus pneumoniae, type I; Bacillus coli; Streptococcus haemolyticus, and Corynebacterium diphtheriae.

A forty-eight hour culture of Staph. aureus grown on veal agar was suspended in a 1 per cent solution of tragacanth U. S. P. in physiologic solution of sodium chloride and introduced intraperitoneally into 40 rats, 28 rabbits and 15 dogs. The tragacanth bacterial suspension was found in previous experiments to induce a marked local inflammatory process.[15] The rats were given one quarter of a billion, the rabbits two thirds of a billion and the dogs 80 billion micro-organisms suspended in 5 cc., 10 cc. and 40 cc. of the tragacanth preparation, respectively. The virulence of the staphylococcus in the dilutions used was of a degree to account for a death rate of from 25 to 50 per cent of the animals in from sixteen to forty-eight hours.

At certain intervals of time the total number of leukocytes per cubic millimeter of peritoneal exudate, the percentages of the different types of white cells and the degree of phagocytosis were determined and frequent cultures were made with exudate obtained either by killing an animal or by abdominal puncture. Smears were stained with the Wright, Gram and methylene blue stains. At each interval of time determinations were made on from 2 to 5 animals.

Table 1 shows the results obtained. In the rat and in the rabbit, the earlier cell picture was overwhelmingly polymorphonuclear, but in the interval from the fifth to the eighth hour, clasmatocytes began to appear and reached, in the rat, 34 per cent of the total number of cells. In the dogs, however, clasmatocytes

13. Freedlander, S. O., and Toomey, J. A.: J. Exper. Med. **47**:663, 1928.
14. Goodpasture, E. W., and Anderson, K.: Am. J. Path. **13**:149, 1937.
15. Steinberg, B., and Goldblatt, H.: Arch. Int. Med. **39**:446, 1927.

never exceeded 6 per cent, the polymorphonuclears being by far the predominant cells. The percentages of these types of cells in the exudate of the rat and the rabbit in the later hours of a staphylococcic peritoneal infection apparently did not conform to those observed in the dog.

In the next set of experiments, the micro-organism used was the pneumococcus, type I. Tragacanth suspensions of forty-eight hour brain broth cultures were

TABLE 1.—*Cell Types in Peritoneal Exudate in Response to Staphylococcic Peritoneal Infection in Normal Rats, Rabbits and Dogs*

	Rat		Rabbit		Dog	
Time After Infection	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	90-100	0	100	0	100	0
3 hr.	94-100	0	100	0	100	0
5 hr.	92	0	98-100	0	100	0
8 hr.	88- 94	1- 6	82- 90	1- 4	98-100	0
12 hr.	76- 94	2-12	82- 92	1- 4	92-100	0
18 hr.	72- 91	8-20	90- 92	1- 2	86- 92	0
24 hr.	52- 82	11-34	88- 90	1- 4	98-100	0
30 hr.	52- 80	13-28	76- 88	6-11	88- 98	0
40 hr.	58- 84	14-32	72- 76	13-15	91- 98	1-2
48 hr.	72- 78	18-21	58- 68	12-18	96- 98	2-4
72 hr.	40- 65	18-32	None survived over 48 hours		92- 98	2-6
96 hr.	31- 40	28-33	.....	.....	86- 92	4-6
5 days	55- 58	4-10	.....	.....	90- 98	2-3
7 days	71- 82	10-12				

TABLE 2.—*Cell Types in Peritoneal Exudate in Response to Type I Pneumococcic Peritoneal Infection in Normal Rats and Dogs*

	Rat		Dog	
Time After Infection	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	100	0	100	0
3 hr.	100	0	100	0
5 hr.	85-88	1- 2	100	0
8 hr.	85-90	0- 1	98-100	0-2
12 hr.	72-84	6-18	100	0
18 hr.	64-77	19-36	100	0
24 hr.	42-76	20-58	94- 96	2-3
30 hr.	32-64	18-46	98-100	0-2
40 hr.	38-49	36-44	98	0-1
48 hr.	52-76	9-21	92- 98	0-1
72 hr.	20-34	50-69	99	0-1
96 hr.	28-49	10-19		
5 days	72-89	8-10	81- 96	2-8

injected intraperitoneally in sublethal quantities (because of decreased virulence and a smaller bacterial population, an older culture was used in larger volumes: 0.5 cc. of culture in 5 cc. of the tragacanth preparation for the rat, and 10 cc. of culture in 40 cc. of the tragacanth preparation for the dog). An occasional animal of each species died in from twenty-four to thirty-six hours. In this experiment 20 rats and 15 dogs were used. As in the previous experiment, either the animals were killed or abdominal punctures were done, and the peritoneal exudate was studied. The rat showed a cell picture in which the clasmatocyte was the dominant type after the eighteenth hour, reaching 69 per cent in seventy-two

hours. On the other hand, the dog consistently and continuously responded with a predominance of the polymorphonuclear cells, the clasmatocyte percentage never exceeding and seldom reaching 8 (table 2).

A set of 10 rats and 5 dogs were given intraperitoneally a tragacanth suspension of a saline washing of a twenty-four hour culture of C. diphtheriae grown on rabbit blood agar. Each rat received 5 cc., containing approximately one quarter of a billion bacteria. The dogs were given 40 cc. of a 1 per cent tragacanth suspension holding approximately 3 billion bacteria. Abdominal punctures were performed on the animals at hourly intervals for the first eight hours and at from six to twelve hour intervals for the next five days. Total white cell counts were made, and smears were made and stained, as in former experiments. The rats showed in from eight to fourteen hours from 4 to 8 per cent clasmatocytes, a proportion which increased to 48 per cent in the fortieth hour. The clasmatocytes varied from 48 to 39 per cent for the next five days. Polymorphonuclears composed the greater part of the remainder of the cells in the exudate.

The dogs, on the other hand, did not show more than 4 per cent clasmatocytes at any time. The polymorphonuclears were the predominant cells in the dog exudate.

Sterile peritoneal exudate obtained from dogs, with a 96 per cent polymorphonuclear content, was introduced intraperitoneally in 10 cc. quantities into 10 rats and 10 rabbits. The peritoneal exudate in the two species of animals showed in from sixteen to twenty hours a clasmatocytic response of 11 per cent in the rats and 24 per cent in the rabbits. In forty hours, the rabbits had 42 per cent; in 66 hours, 56 per cent. The rats showed persistently lower clasmatocyte counts.

Tragacanth suspensions of cultures of the colon bacillus or of cultures of the hemolytic streptococcus were injected intraperitoneally into 5 rabbits and 5 dogs. Studies of the peritoneal exudate revealed a clasmatocytic response to each of the micro-organisms injected in the rabbit within eighteen hours. The number of clasmatocytes increased in succeeding hours, reaching from 44 to 50 per cent in ninety-six hours. On the other hand, the dogs at no time showed more than from 6 to 8 per cent clasmatocytes, the cellular content being predominantly polymorphonuclear.

Comment.—The cellular character of the exudate in the later stages of an acute inflammatory process of the peritoneum varies with the species of animal. The normal albino rat and the rabbit without known enhanced resistance respond with a considerable number of clasmatocytes (proliferating fixed tissue cells) in the later hours of inflammation. The normal dog, on the other hand, at no time during the inflammatory process of the peritoneum shows the presence of an appreciable number of clasmatocytes, the predominant cell being invariably the polymorphonuclear.

Variation of the species of micro-organism used (B. coli, Staph. aureus, D. pneumoniae, Str. haemolyticus, C. diphtheriae) did not alter this difference of cellular response in the animals. When dog polymorphonuclears are injected intraperitoneally into rats and rabbits, these animals respond by rapid clasmatocytosis, the percentage of the clasmatocytes being greater (in the rabbit) than observed in inflammation due to micro-organisms. This observation may suggest that some fac-

tor in the polymorphonuclear may have a stimulating effect on proliferation of clasmatocytes and their attraction to the inflammatory field.

It is significant that irrespective of the animal species the first overwhelmingly predominant cells were consistently the polymorphonuclears. In previous experiments [16] it was shown that the outcome in a massive peritoneal infection is decided in the first eight to twelve hours after the bacterial invasion. In the light of the former experiments, it may be assumed that the polymorphonuclear is the only phagocytic cell responsible for the removal of micro-organisms (used in these experiments) and that the polymorphonuclear is the essential cell in the local struggle of an acute inflammatory process due to bacterial invasion.

TABLE 3.—*Cell Types in Pleural Exudate in Response to Staphylococcic, Pneumococcic and Colon Bacillus Pleural Infection in Normal Dogs and Rabbits*

	Dog						Rabbit					
	Staph. Aureus		Pneumococcus, Type I		B. Coli		Staph. Aureus		Pneumococcus, Type I		B. Coli	
Time After Infection	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %
8 hr.	99	1	100	0	100	0	100	0	98	1	100	0
18 hr.	94	6	100	0	99-100	0-1	96	4	97	3	100	0
30 hr.	99-100	0-1	100	0	92- 99	1-8	91-93	7- 9	99-100	0-1	85- 99	1-15
48 hr.	100	0	99-100	0-1	92-100	0-8	78-82	18-22	None lived		88- 98	2-12
72 hr.	98-100	0-2	None lived		91-100	0-9	88-94	6-18	up to 48 hours		91- 98	2-9
5 days	95-100	0-5	to 72 hours		94-100	0-6	90-93	7-10			97-100	1-3
6 days	99-100	0-1			93- 96	4-7	71-76	22-27			92- 96	4-8
7 days	99-100	0-1			90- 91	9-10	72-74	21-27			72- 85	28-15

VARIATION OF ANIMAL SPECIES AND BACTERIAL TYPES IN THE PRODUCTION OF INFLAMMATION OF PLEURAL SEROSA

In the following experiments, normal dogs and rabbits were given intrapleural injections of the following micro-organisms: Staph. aureus; D. pneumoniae, type I; B. coli, and Str. haemolyticus. The numbers of the micro-organisms injected were the same as injected intraperitoneally in the experiments described, but the volume of the tragacanth suspension medium was less, 5 cc. for the rabbit and 20 cc. for the dog. Five animals of each species were used for each of these types of micro-organisms. Differential cell counts and bacterial culture studies were made on exudate obtained by chest punctures. The pneumococcus culture employed was sufficiently virulent to induce death in all of the animals given it in from thirty to seventy-two hours. All of the animals given staphylococcus culture survived. Of the animals given cultures of B. coli, 1 dog and 3 rabbits died in from six hours to seven days. After the eighteenth hour, the rabbits apparently died because of the presence of large volumes of exudate and fibrin in the pleural cavities and consequent compression of the lungs.

16. Steinberg, B., and Snyder, D. A.: Arch. Path. **8**:419, 1929.

Irrespective of the micro-organism employed, the cellular response in the normal pleural cavity of the dog was predominantly polymorphonuclear, with clasmatocytes appearing in the thirtieth hour but never exceeding 10 per cent (table 3).

The cellular response in the pleural cavity of the rabbit was predominantly polymorphonuclear in the early hours. After the thirtieth hour, clasmatocytes began to appear and eventually composed as much as 56 per cent of the total number of cells. The greatest clasmatocytic response was obtained with Str. haemolyticus infection, the organism being only mildly virulent (tables 3 and 4).

Comment.—As was true in peritoneal infection, normal dogs responded to intrapleural infection with the bacteria used in these experiments by a predominantly polymorphonuclear exudate. Normal rabbits, on the other hand, showed in the later hours of the inflammatory process a considerable number of clasmatocytes. It appears that a somewhat greater number of clasmatocytes appear in the pleural than in the peritoneal exudate, this being especially true in rabbits.

TABLE 4.—*Cell Types in Pleural Exudate in Response to a Pleural Infection with Str. Haemolyticus in Normal Rabbits*

Time After Infection	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	97-100	0
3 hr.	97	0
5 hr.	94- 98	0- 2
8 hr.	94-100	0- 3
12 hr.	92- 98	0- 4
18 hr.	94-100	0- 4
24 hr.	92- 94	2- 6
30 hr.	88- 96	4- 9
40 hr.	80- 86	7-12
48 hr.	72- 84	11-15
72 hr.	29- 35	50-56
96 hr.	30- 38	41-54

RELATION OF CELL TYPE TO ENHANCED RESISTANCE

Enhanced resistance to a given micro-organism was induced in four ways: First, five graduated doses of a heat-killed culture of Str. haemolyticus suspended in saline solution were introduced intrapleurally over a period of two weeks, and five days after the last vaccination a viable and virulent culture of Str. haemolyticus suspended in the tragacanth preparation was injected intrapleurally. The second method consisted in the introduction of sublethal viable cultures of Staph. aureus and of B. coli intrapleurally, followed in one week by a tragacanth preparation of a culture of the same bacteria, previously demonstrated to be lethal. The third method was to induce a local intraperitoneal accumulation of leukocytes by the injection of a "leukocyte-evoking antigen," described elsewhere.[17] The fourth method consisted in the intraperitoneal introduction of pneumococcus antiserum, type I, from one to three hours after the injection of a culture of the homologous pneumococcus suspended in the tragacanth preparation, into the peritoneal cavity. The criterion of success in the attempt to induce enhanced resistance consisted in survival of at least 75 per cent of the animals. The relationship of the cell picture of the exudate to bacterial invasion was studied by withdrawing with a glass capillary pipet fluid from the chest and from the peritoneal cavity and

17. Steinberg, B.: Am. J. Clin. Path. **6**:253, 1936.

determining the cell type, the presence of free bacteria, the degree of phagocytosis, and the persistence of viable intracellular bacteria by culture. Dogs, rabbits and rats were used in this experiment.

In a group of 10 dogs, a peritoneal leukocyte exudate was induced by the introduction of the "leukocyte-evoking antigen," [17] and forty-eight hours later one

TABLE 5.—*Cell Types in Peritoneal Exudate in Response to a Peritoneal Infection with Pneumococcus or Colon Bacillus in Dogs with Artificially Enhanced Resistance*

	Pneumococcus Infection*				Colon Bacillus Infection:* Hyperleukocytosis Locally Induced	
	Antiserum Given Intraperitoneally Shortly After Infection		Hyperleukocytosis Locally Induced			
Time After Infection	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	100	0	100	0	100	0
3 hr.	100	0	100	0	100	0
5 hr.	100	0	100	0	100	0
8 hr.	100	0	100	0	100	0
12 hr.	100	0	100	0	100	0
18 hr.	100	0	96	0	100	0
24 hr.	99	1	92-96	3	100	0
30 hr.	99-100	0- 1	92	1-3	96-100	0- 4
40 hr.	99-100	0- 1	92-98	1-2	92- 96	0- 5
48 hr.	95-100	0- 5	99	1	94- 99	1- 3
72 hr.	95-100	0- 5	88-90	1-6	90-100	0- 7
96 hr.	82- 80	0- 2	82-90	0-8	82- 96	4-11
5 days	78- 81	2- 8	82-86	4-6	90- 98	2- 7
7 days	79- 81	5-16	80-91	1-5	88- 94	2-12

* Prior to induction of the infection, the cell picture showed from 81 to 90 per cent polymorphonuclears and from 2 to 9 per cent clasmatocytes.

TABLE 6.—*Cell Types in Pleural Exudate in Response to a Pleural Infection with Str. Haemolyticus, Staph. Aureus and B. Coli, in Dogs with Artificially Enhanced Resistance*

	Local Vaccination* with					
	Str. Haemolyticus		Staph. Aureus		B. Coli	
Time After Infection	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	94- 97	0-4				
3 hr.	95-100	0-1				
5 hr.	97-100	0	96-100	0-4	100	0
8 hr.	95-100	0-3	94- 98	2-6	100	0
12 hr.	98-100	0-2	96-100	0-4	95- 98	2-5
18 hr.	100	0	96-100	0-2	99-100	0-1
24 hr.	100	0	100	0	93- 95	5-7
30 hr.	.....	...	100	0	99-100	0-1
40 hr.	98- 99	1-2				
48 hr.	98-100	0-2	100	0	100	0
72 hr.	.....	...	100	0	100	0
96 hr.	95- 96	2-4				
5 days	97- 99	0-1	98	2	98	2

* Prior to induction of the infection, the cell picture of the pleural exudate showed from 79 to 92 per cent polymorphonuclears and from 5 to 11 per cent clasmatocytes.

group of 5 dogs was infected by injection of pneumococci of type I and the other group of 5 dogs by injection of colon bacilli suspended in the tragacanth preparation as described. In a third group of 5 dogs a homologous horse pneumococcus antiserum (20,000 units) was injected intraperitoneally three hours after the injection of the culture of the type I pneumococcus.

Three groups of 5 dogs each were prepared by intrapleural vaccination with a heat-killed culture of Str. haemolyticus, a sublethal viable culture of Staph. aureus

and a culture of B coli, respectively, and the 15 animals were later subjected to reinjection of a viable virulent culture of the corresponding micro-organism suspended in the tragacanth preparation as described.

Prior to the introduction of the viable virulent bacteria, the cell composition of the exudate in the dogs was determined to vary between 79 and 92 per cent polymorphonuclears and between 2 and 11 per cent clasmatocytes.

Subsequent examinations of the peritoneal or pleural exudate of the dogs following infection with the viable virulent micro-organisms mentioned revealed a

TABLE 7.—*Cell Types in Pleural Exudate in Response to a Pleural Infection with Str. Haemolyticus in Rabbits with Resistance Enhanced by Local Vaccination**

Time After Infection	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	88- 92	4- 8
3 hr.	91- 96	0- 5
5 hr.	90-100	0- 2
8 hr.	88- 92	8-12
12 hr.	86- 90	2- 5
18 hr.	97-100	0- 3
24 hr.	92- 96	1- 5
30 hr.	90- 92	8-10
40 hr.	30-100	0-54
48 hr.	27- 42	18-36
72 hr.	15- 46	20-40
96 hr.	11- 22	58-72

* Prior to induction of the infection, the cell picture of the pleural exudate showed from 48 to 54 per cent clasmatocytes and from 30 to 36 per cent polymorphonuclears.

TABLE 8.—*Cell Types in Peritoneal Exudate in Response to a Peritoneal Infection with Type I Pneumococcus in Rats with Resistance Enhanced by Introduction of the Homologous Antiserum*

Time After Infection and the Introduction of Serum	Polymorphonuclears, %	Clasmatocytes, %
1 hr.	92-100	0- 8
5 hr.	86- 98	2-14
12 hr.	72- 80	13-21
18 hr.	77- 79	11-19
24 hr.	58- 59	32-37
30 hr.	52- 61	40-49
40 hr.	49	40-44
48 hr.	41- 50	38-40
72 hr.	30- 52	34-58
96 hr.	8- 29	40-82
5 days.	11- 36	28-42
7 days.	10- 89	10-90

preponderating polymorphonuclear content, with clasmatocytes at no time reaching more than 12 per cent (tables 5 and 6). It was observed that following the onset of infection the polymorphonuclears rapidly increased in number and that the large number of these cells persisted as long as free bacteria were present and as long as cultures remained positive.

A group of 12 rabbits were vaccinated intrapleurally with heat-killed cultures of Str. haemolyticus as described. Prior to infection with viable bacteria, the exudate in the chest contained from 48 to 54 per cent clasmatocytes and from 30 to 36 per cent polymorphonuclears. The cell types were determined for ninety-six hours after onset of the infection on exudate obtained by puncture of the wall of the chest with a glass capillary pipet or by killing an animal. In the first five hours,

the percentage of the polymorphonuclears increased from 88 to 100 owing to an absolute increase in the total number of cells (table 7). During the stage of polymorphonuclear predominance, free and phagocytosed bacteria were present in the smears, and the cultures were positive. The clasmatocytic increase corresponded to disappearance of free bacteria and marked diminution in the number of bacterial colonies or absence of colonies in the cultures of the exudates.

Each of 15 rats was given an injection of a culture of Pneumococcus, type I, suspended in the tragacanth preparation as described. One hour later, each rat was given intraperitoneally 5,000 units of the homologous antiserum. The polymorphonuclear content of the peritoneal exudate within the first five hours varied from 92 to 100 per cent, but from that time on clasmatocytes appeared in increasing numbers. In twenty-four hours, the clasmatocytes formed from 32 to 37 per cent of the total number of cells, and in some of the animals they constituted on the seventh day as much as 90 per cent (table 8).

Correlation of the cell type to bacterial invasion disclosed the persistence of large numbers of polymorphonuclears coincident with the presence of free bacteria.

Comment.—Enhanced resistance, whether of the active or of the passive type, tended to be associated with a slight increase in the number of clasmatocytes in the pleural and peritoneal exudates of dogs receiving injections of cultures of Pneumococcus, type I, B. coli, Str. haemolyticus and Staph. aureus. The polymorphonuclear remained, however, the predominant cell.

On the other hand, both the rabbit and the rat showed a definite increase in the number of clasmatocytes in the presence of enhanced resistance. This clasmatocytic increase was associated with a disappearance of free bacteria in the exudate and a diminution in the number of clasmatocytes in the presence of enhanced resistance. This clasmatocytic increase was associated with a disappearance of free bacteria in the exudate and a diminution in the number of bacterial colonies in the cultures. The larger clasmatocytic percentage of the total number of cells associated with recovery has been apparently erroneously interpreted by investigators to indicate the importance of that cell in combating invading bacteria in acute infections. These studies reveal that polymorphonuclears ingest invading bacteria very early (in the first five to eighteen hours), and the absence of free bacteria and the subsequent successful intracellular digestion of the micro-organisms determine the numerical appearance of clasmatocytes. Consequently, clasmatocytes appear, not in response to bacterial invasion, but rather as a result of removal of the bacteria by the polymorphonuclears.

SUMMARY

In the dog the predominant cell in the peritoneal or pleural exudate of an acute inflammatory process under the conditions of these experiments is the polymorphonuclear. The clasmatocyte (macrophage) forms a negligible factor.

In the rabbit and more so in the rat, the clasmatocyte appears in large numbers. This type of cell appears, however, either in the terminal period or after the struggle between the body's defense and the micro-organism is complete. Enhanced resistance (active and passive) evokes clasmatocytes in the rat and in the rabbit more quickly and in a larger number than in the dog. In the dog, any increase in these cells is negligible. In those animals, whether dogs, rabbits or rats, in which clasmatocytosis has been induced by enhanced resistance, the polymorphonuclears reappear in predominant numbers and phagocytose the invading bacteria.

It is assumed from these studies that the clasmatocyte is not a factor in defense in acute inflammation produced by micro-organisms and under the conditions of these experiments.

Dog polymorphonuclears introduced into the peritoneal cavities of rabbits and rats induced in the rabbits proliferation of clasmatocytes more rapidly and in a larger number than a staphylococcic infection did. The rats showed a lower percentage of clasmatocytes. It may be suggested that in these experiments some factor in the polymorphonuclear may possibly supply the stimulus to proliferation of fixed tissue cells and attraction to the inflammatory field.

LOSS OF ACIDOPHILIC GRANULES FROM THE PITUITARY OF THE GUINEA PIG UNDER EXPERIMENTAL CONDITIONS OF INCREASED METABOLISM

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In studying the pituitaries of cats which were the subject of experiments carried out by Long and Lukens,[1] it was observed that loss of acidophilic granules from the pituitaries was a conspicuous feature in some of the animals. Since in each instance the pancreas and both adrenals had been removed and adrenal cortical extract administered, and in some instances anterior pituitary extract given as well, it was impossible to say whether the operations or the injections or both were factors in determining the degranulation. When in the course of experiments on the thyrotropic factor of the pituitary a loss of acidophilic granules of much the same character was encountered in the pituitaries of guinea pigs given injections of rat pituitaries, a systematic experimental and histologic study of such pituitaries was begun.

EFFECT OF INJECTED RAT PITUITARIES ON THE PITUITARIES OF THE RECIPIENT GUINEA PIGS

Experimental Procedure.—The first experiments consisted of the study of the pituitaries of the guinea pigs used as the test animals in determining quantitatively the thyrotropic content of pituitaries from thyroidectomized rats as compared with those from normal rats.[2] The method of injection was given in the published report of these experiments and, briefly, consisted of injecting daily into each guinea pig the fresh pituitary of a thyroidectomized rat until three or four pituitaries had been injected, while other guinea pigs were treated similarly with the pituitaries of normal rats of the same sex and age. The guinea pigs were females weighing between 150 and 200 Gm. They were killed twenty-four hours after the last injection and the pituitaries promptly fixed in Helly's solution. Untreated guinea pigs were used as controls.

Twenty-two guinea pig pituitaries were examined histologically, in the following grouping: three from guinea pigs into which the pituitaries of eleven female thyroidectomized rats had been injected; three from guinea pigs into which the pituitaries of eleven female normal rats had been injected; three from guinea

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1. Long, C. N. H., and Lukens, F. D. W.: J. Exper. Med. **63**:465, 1936.
2. Zeckwer, I. T.: Am. J. Physiol. **117**:518, 1936.

pigs which received the pituitaries of twelve thyroidectomized male rats; four from guinea pigs which were given the pituitaries of sixteen normal male rats, and nine from guinea pigs which were not given injections. The guinea pigs that received the injections showed characteristic stimulation of their thyroid glands and loss of body weight.

Microscopic sections of the pituitaries from these animals were mounted on the same slide with a section of the pituitary of an untreated control guinea pig so as to insure that the experimental and the control pituitaries were subjected to exactly the same staining technic, thus permitting valid interpretations of the comparative staining of chromophilic granules. In passing, it might be emphasized that failure to control staining in this way in all probability accounts for many discrepancies in the published descriptions of histologic changes in the pituitary under various conditions. In addition, serial sections were made of the pituitaries of twelve of the guinea pigs to insure that any changes observed were not occurring merely at a single level. All the sections were stained with Mallory's acid fuchsin, orange G method.

Results.—The pituitaries of the guinea pigs that were given injections showed conspicuous decrease of acidophilic granules. The sections had a pale, washed-out appearance, while on the same slide the pituitary of the untreated control showed intense brilliant red staining of granules. The loss of granules occurred in a patchy manner, groups of cells retaining many granules alternating with bald areas containing only a few scattered granules stained very palely. The cell bodies which contained only a few granules were much larger, sometimes twice as large as the body of the normal small compact acidophilic cell that is crowded with granules. These degranulated acidophilic cells resembled chromophobe cells in size and character of cytoplasm and in staining properties except for the presence of the few remaining acidophilic granules. It should be noted that the view is accepted by many workers that the chromophobe cell differentiates to the acidophilic ceil and that the latter can revert by dedifferentiation to the chromophobe state.

In two groups of experiments the pituitaries of guinea pigs given injections of thyroidectomized rats' pituitaries showed greater loss of granules than did those given injections of normal rats' pituitaries, while in three groups of experiments, the reverse occurred.

The changes in the acidophilic cells were too obvious to necessitate counts. When the sections were repeatedly examined without knowledge as to which were those of the animals that had received injections and which were those of the controls, they were correctly separated on a histologic basis without a single error.

In one series the guinea pig pituitaries were weighed, and the animals given injections were found to have pituitaries lighter than those of the controls. When the ratio of pituitary weight to kidney weight was determined in order to correct for differences in the size of the animals and for the varying degrees of loss of subcutaneous tissues, the value for a guinea pig given injections of thyroidectomized rats' pituitaries was 0.0028, that for a guinea pig given injections of

normal rats' pituitaries was 0.0023, and those for the two untreated controls were 0.0033 and 0.0041.

Franck [3] found that at three selected intervals (sixteen minutes, from one to two hours and from three to four days) after the injection of an alkaline extract of beef pituitary into adult male guinea pigs the typical acidophilic cells were reduced in number, while what he calls hypo-acidophilic and small acidophilic cells were increased in number. Typical basophilic cells disappeared, while small basophilic cells increased. Chromophobe cells increased. He interpreted the changes as an interruption or suspension of the normal cycle of the development of the cells, with an arrest in the formation of typical acidophilic cells.

Collip, Selye and Thomson [4] injected daily into female rats pituitary extracts rich in thyrotropic substance but containing also gonadotropic substance. After from six to ten weeks the ovaries had involuted, and the pituitary contained cells like castration cells, hemorrhages and cysts. In view of the ovarian atrophy, many of the histologic changes which the authors observed might be interpreted as castration effects.

When whole pituitary is injected, all the factors in the injected material must be considered as possible agents in producing changes in the various peripheral endocrine organs. Furthermore, these glands, being in this manner stimulated to secrete their own principles, will in turn affect the pituitary in the manner described in the voluminous literature on histologic changes in this gland following injection of ovarian and other substances. Since the rat pituitary is especially potent in thyrotropic substance and the female guinea pig's thyroid is especially sensitive in its response to this factor, the thyrotropic substance was thought to be the most likely factor in producing the changes of the present experiments. Accordingly, the hypothesis was tentatively made that the thyroid secretion liberated by the guinea pig's thyroid after it has been stimulated by the injected rat pituitary was the factor affecting the histologic character of the guinea pig's pituitary.

To test this hypothesis, experiments were carried out to determine the effect on the pituitary of the guinea pig of feeding thyroid extract to the animal.

EFFECT OF FEEDING THYROID EXTRACT ON THE PITUITARY OF THE GUINEA PIG

Experimental Procedure.—Seven male and five female guinea pigs were fed desiccated thyroid extract in aqueous suspension by pipet introduced into their

3. Franck, S.: Compt. rend. Soc. de biol. **119**:419, 1935.

4. Collip, J. B.; Selye, H., and Thomson, D. L.: Proc. Soc. Exper. Biol. & Med. **31**:682, 1934.

mouths. The total dose varied from 0.325 to 2.6 Gm. over periods varying from four to fourteen days. They were killed with chloroform, and their pituitaries were promptly fixed in Helly's solution. Sections of three normal guinea pig pituitaries were mounted on the same slides with the experimental ones and stained simultaneously with Mallory's stain.

Results.—The pituitaries of the thyroid-fed guinea pigs showed acidophilic cells that had become markedly degranulated. The loss of acidophilic granules, as well as the entire histologic picture, was identical with that seen in the guinea pigs that were given injections of rats' pituitaries.

No records were found in the literature of previous experiments of this nature on guinea pigs.[4a] The effect of thyroid feeding on rats' pituitaries, however, has been reported by Kojima,[5] who found a decrease in acidophilic cells. Sevringhaus, Smelser and Clark[6] found in male rats which had been fed thyroid extract daily for thirty days atrophy of accessory reproductive organs, castrate in type, and in the pituitary gland basophilic castration cells and acidophilic cells larger and more brilliant than usual, while Campbell, Wolfe and Phelps[7] in female rats fed thyroid daily for from thirty to seventy-one days found the basophilic cells larger and packed with granules and the acidophilic cells moderately reduced in number in some cases. Cohen[8] found basophilic cells increased in thyroid-fed rats. Various workers have found loss of weight of the pituitary after thyroid feeding. Since there are so many species differences in the sensitiveness of reaction to hormones and since varying effects might be expected from varying dosage, the discussion will be limited to the conditions of the present experiments. In these guinea pigs the experimental conditions were not continued long enough to cause atrophy of the gonads.

The meaning of the loss of acidophilic cells was not clear, but the following line of reasoning was considered: There is abundant evidence that the acidophilic cells elaborate a factor promoting growth. It seems reasonable to suppose that this factor is not merely concerned with abnormal growth, as in gigantism and acromegaly, and with abnormal dwarfing, but that normal maintenance of visceral weights may depend

4a. Since the writing of this article, it has been found that S. Franck (Compt. rend. Soc. de biol. **123**:335, 1936) described degranulation of acidophils in the guinea pig pituitary following administration of desiccated thyroid.

5. Kojima, M.: Quart. J. Exper. Physiol. **11**:319, 1917.

6. Sevringhaus, A. E.; Smelser, G. K., and Clark, H. M.: Proc. Soc. Exper. Biol. & Med. **31**:1125, 1934.

7. Campbell, M.; Wolfe, J. M., and Phelps, D.: Proc. Soc. Exper. Biol. & Med. **32**:205, 1934.

8. Cohen, R. S.: Am. J. Anat. **56**:143, 1935.

on it and that it may permit the regeneration which replaces normal catabolism and maintains growth equilibrium. When the pituitary is massively destroyed, as in Simmond's disease, one sees not only failure of growth but atrophy of nonendocrine viscera. In increased catabolism

Fig. 1.—Pituitary of a normal female guinea pig that was gaining weight (control); ×640. The acidophilic cells are seen as very small dark cells. The granules are so closely packed in the cytoplasm that they appear as a dark rim around the nucleus. These cells constitute nearly 50 per cent of all the cells. The chromophobe cells are much larger, paler cells. The magnification and optical setup are exactly the same as for figures 2 and 3.

and loss of tissues as seen in the guinea pig after excessive feeding of thyroid extract or after injections of rat pituitaries which stimulate the recipient's thyroid to hypersecretion, there may be an extra demand

placed on the pituitary for secretion by it of the substance influencing growth in order that growth may be accelerated and equilibrium restored.

When a pituitary shows increased granulation of its basophilic cells, as after castration in rats, such a change is thought to represent

Fig. 2.—Pituitary of a female guinea pig into which the pituitaries of four normal male rats had been injected; × 640. The loss of body weight was 18 Gm. A degranulated area is shown. Few of the small, compact normal acidophilic cells remain. In the black and white photograph the enlarged degranulated acidophilic cells cannot be distinguished from chromophobe cells.

increased, active secretion of gonadotropic substance as a compensatory phenomenon, this being indicated by quantitative determinations carried out by several workers, who found increased content of gonadotropic

substance in the pituitaries of castrate rats and increased secretion into the blood stream. Conversely, degranulation of secretory cells of the pituitary may be like degranulation of secretory glands with ducts, such as the pancreatic acini, in which case degranulation is accepted by many

Fig. 3.—Pituitary of a female guinea pig that was fed a total of 1.1 Gm. of desiccated thyroid extract over a period of fourteen days; × 640. The loss of body weight was 44 Gm. The acidophilic cells have become largely degranulated, the cell size has enlarged, and the cytoplasm has become almost as clear as in normal chromophobe cells.

histologists as evidence of more or less complete discharge and exhaustion of secretory products. In other words, when secretion is active and adequate to the demands, a secretory cell is full of granules; when it is exhausted by excessive demands, it is depleted of secretory granules.

Consequently, it is logical to consider the possibility that loss of acidophilic granules represents exhaustion after excessive release of the factor influencing growth which has occurred in a compensatory attempt to restore growth in an animal in which tissues were wasting with the increased catabolism resulting from excess of thyroid secretion (whether formed by the animal's own thyroid or introduced from another animal source).

It seems reasonable to suppose that the state of the acidophilic cells may vary with the intensity of the demand for the substance promoting growth. A slight need over a long period might lead to compensatory hyperplasia of acidophilic cells, whereas a sudden extreme demand, as in the present experiments, might lead to discharge of all the available secretion and disappearance of acidophilic granules.

COMMENT

The theory suggested here seems at first to be incompatible with the fact that there is extreme loss of acidophilic cells in the pituitaries of thyroidectomized animals. In fact, the degree of acidophilic loss in the pituitaries of rats that were thyroidectomized at an early age [9] was roughly proportional to the retardation in the growth of the viscera. That is, both excessive thyroid secretion and complete lack of thyroid secretion are associated with the same loss of acidophilic cells. But this does not seem an inconsistency when one considers that in the animal dwarfed by thyroidectomy there is need of all available growth principle to restore equilibrium, and that all of this principle which is available is discharged by the acidophilic cells that still exist, and hence their degranulation. I have previously stated that the dwarfing of the cretin rat was probably due to loss of the acidophilic cells. In view of the present experiments and interpretation, the previous opinion might be modified to the suggestion that dwarfing of the cretin rat is associated with lack of acidophilic cells, which may indicate that the cretin pituitary has discharged all the growth factor which it is capable of producing, and that there has been a fault in adequate production of acidophilic cells and hence a failure to establish equilibrium. In reality, it seems necessary to assume that there is a failure to produce normal acidophilic cells. The modification of the original view is merely the assumption that there is as well an increased demand for the factor promoting growth, which depletes the existing acidophilic cells of their secretion.

The explanation suggested here is entirely tentative and is quite apart from the recording of the objective data in these experiments. It

9. Zeckwer, I. T.; Davison, L. W.; Keller, T. B., and Livingood, C. S. II: Am. J. M. Sc. **190**:145, 1935. Zeckwer, I. T.: Am. J. Path. **13**:985, 1937.

would be indeed rash to apply these ideas to the human being or to take them as an indication for therapeutic measures. They are intended to be of purely theoretical interest, with full realization that there are many species differences in endocrine reactions. In a field in which unsubstantiated speculations have been too prevalent in the past, it is likely that these explanations may prove wrong. Whether or not the interpretation suggested here is correct, the common factor in all the experiments was increased catabolism. This raises the question whether the loss of acidophilic granules in the cats of Long and Lukens, which was the starting point of these experiments, may have been a depletion of the principle affecting growth as a result of loss of body weight after combined adrenalectomy and pancreatectomy.

It is evident that the pituitary shows as much structural lability as does the thyroid, striking cellular changes occurring in short intervals of time.

There remains the possibility that loss of acidophilic granules may represent atrophy from disuse. It is well known that when a normal animal is fed thyroid, its own thyroid goes into a state of rest, since there is no need for this organ to secrete when the animal is being supplied with an excess from an outside source. Perhaps the alteration in character of the acidophilic cells after feeding thyroid substance and after injection of the thyrotropic factor of the pituitary represents atrophy from disuse when an excess of thyroid hormone circulating in the body stops the demand for pituitary production of the thyrotropic factor. If that should be so, it would point to the acidophilic cell as the elaborator of the thyrotropic factor. However, the pituitaries of cretin rats, showing almost no acidophilic cells, contain large amounts of the thyrotropic factor,[10] which excludes the acidophilic cell as the producer of this factor and makes improbable the conception that the loss of acidophilic cells in the pituitary of the cretin is due to atrophy of the cells producing the thyrotropic factor, through disuse.

SUMMARY

Loss of acidophilic granules occurred in the pituitaries of guinea pigs (*a*) after injection of pituitaries from normal and thyroidectomized rats and (*b*) after feeding of thyroid. It is suggested that this may represent discharge from the guinea pig's pituitary of the growth principle under conditions of increased metabolism.

10. Zeckwer, I. T.: Am. J. Physiol. **117**:518, 1936.

BRONCHIOGENIC DISTRIBUTION OF FLUID AND PARTICULATE MATTER

ITS SITE OF PREDILECTION AND THE MECHANISM OF TRANSFER

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Bronchiogenic distribution of particulate matter is generally said to affect the base of the lungs by preference. Nevertheless the spread of pulmonary tuberculosis, which in man takes place largely by the bronchial route, extends in the classic "craniocaudal progression." Thus the base is the last portion of the lung to be involved unless, as is usually true, the patient dies in earlier stages of the disease. Furthermore, in translateral extension the lesions are found in the cranial rather than in the caudal parts of the lung.

In order to study the matter further, the lungs from 102 unselected routine autopsies in cases of pulmonary tuberculosis, pneumonoconiosis or a combination of the two diseases were examined. In 85 cases, the disease was diffuse, but in 50 instances the lesions were confined to restricted areas of obvious predomination. This group of 50 cases was selected for detailed study. In 27 instances (over 50 per cent) the lesion was observed as a transverse band, which occupied on the right the lower third of the upper lobe and the apex of the lower lobe, and on the left the middle third of the upper lobe and the apex of the lower lobe. This area may be involved in part or throughout its entire extent. In 11 instances, only the apexes of the upper lobes were diseased. The base of the lung was affected in only 6 instances, and in 6 other instances the lesions were found in miscellaneous locations.

There is therefore an obvious predilection for a part of the lung which will be termed the transverse band area. In lungs in which this area alone is affected, the outline is sharp, and the shape is often somewhat conical, with the apex near the hilus and the base reaching into the peripheral parenchyma or even to the pleura. The configuration of this lesion was exactly reproduced in the upper lobes of human lungs removed at autopsy by injecting an opaque substance into the caudal and dorsal branches of the bronchus eparterialis on the right and the bronchus ventralis on the left. The parts of the lesion in the apexes

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of the lower lobes were duplicated by injecting the opaque substance into the first dorsal branch of the main stem bronchus hyparterialis.

The assumption that the lesion is produced by bronchiogenic distribution is strengthened by experiments on animals. Guinea pigs and rabbits into whose tracheas small amounts of india ink were injected showed deposition of the pigment in the transverse band area either exclusively or preponderantly.

The rabbit is the animal of choice, since in the guinea pig the small size of the respiratory tract increases the risk of flooding the entire bronchial system. The animal is anesthetized with ether until the cough reflex is entirely eliminated. The trachea is then dissected free from surrounding tissues, and from 0.1 to 0.2 cc. of undiluted india ink is injected into the lumen, about 1 cm. above the sternoclavicular joint. A needle of not more than 25 by 0.62 mm. should be used. After from three to five minutes the animal is killed by ether inhalation or by bleeding, never by any method which will produce gasping respiration; the trachea is clamped, and the lungs are removed. In most instances the india ink will be found deposited directly below the pleura of the transverse band area. In some cases it is seen only on making a coronal incision of the formaldehyde-fixed organ (fig. 1). The best demonstration is obtained by clearing with the Spalteholz method (fig. 2).

There is no conceivable hematogenous mechanism by which this lesion could be produced, particularly bilaterally. Localized miliary tuberculosis of a lobe can occur when tuberculosis of a node or of the parenchyma of the lung invades a branch of the pulmonary artery. Such lesions were searched for in the autopsies mentioned but were never demonstrated. Moreover, the vessels of the different parts of the transverse band area do not supply this area exclusively. The distribution of tuberculosis in the lung of a person suffering from chronic pulmonary tuberculosis with cavitation occurs predominantly by way of the bronchi.

While it must therefore be accepted that the transverse band area is involved by the bronchiogenic route, the mechanism is demonstrable only with difficulty. Gravity alone is not a sufficient cause for the phenomenon. Whether the animal is placed in the dorsal or in the supine position or held upright during and after injection, the carbon is deposited in some part of the transverse band area. The supine position tends to fill the mediastinal and the ventral portion of the transverse band area, including portions of the right middle lobe, whereas the dorsal position causes the india ink to appear in the vertebral portion. At all events, the same general field is affected. No striking differences between the right and left sides were observed, unless the animal was placed in the lateral position.

The anatomy of the bronchial tree is such that the dorsal, or membranous, portion is not flat, as is commonly asserted in textbooks, but shows two lateral grooves separated by a raised longitudinal fold (fig. 3).

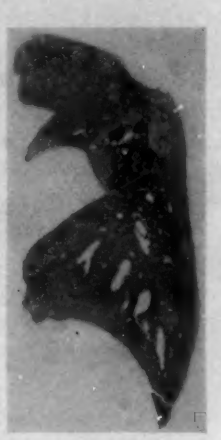

Fig.1.—Coronal section of a rabbit's lung showing a deposit of india ink in the transverse band area.

Fig. 2.—Spalteholz preparation of a rabbit's lungs after an injection of india ink, dorsal view.

At the carina the fold forks and passing down the main bronchi repeats the conformity of two lateral grooves between which is a raised fold. This process is repeated at each bronchial ostium.

In the bronchi, however, the external lateral groove is broader and deeper than the internal lateral. Moreover, the external lateral groove of each bronchus passes uninterruptedly into the external lateral groove of the most lateral bronchial branch whereas all other grooves and bronchi are interrupted by the central elevated fold. Thus there is a system of lateral grooves continuous with the two lateral grooves of the trachea. These folds and grooves are not as easily demonstrable in

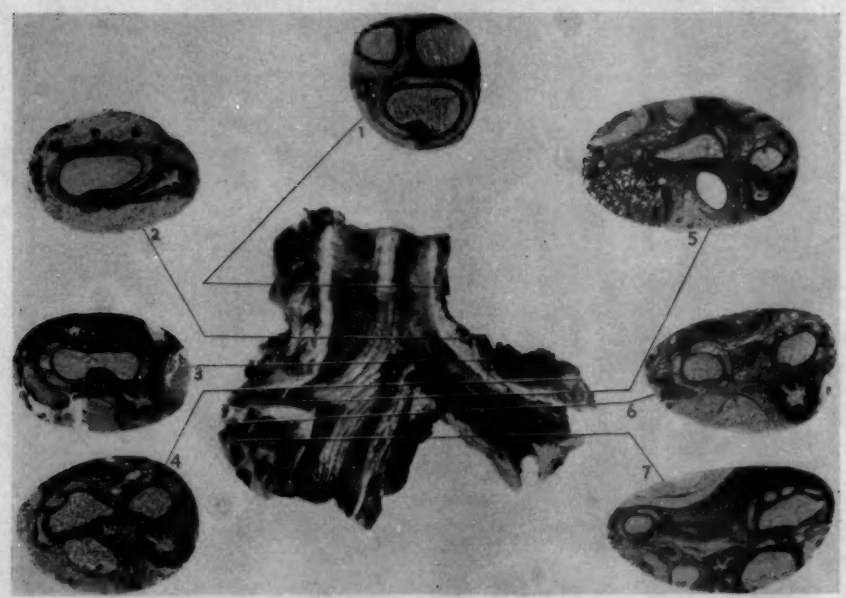

Fig. 3.—Human adult trachea and bronchi (opened ventrally) with cross sections of the trachea and bronchi of a newborn infant.

man as in the laboratory animal, probably because of the effect of disease and postmortem changes. Thus Macht and Giu-Ching Ting [1] noted a distinct difference between the pharmacologic reactions of bronchial muscle taken from animals suffering from pneumonia as contrasted with the muscle taken from normal animals. At autopsy the best specimens are obtained if the bronchial tree is given an injection of formaldehyde soon after death. The grooves cannot be demonstrated by the use of plaster of paris and Wood's metal casts, since the expansion of these materials on hardening destroys the natural contour of the

1. Macht, D. I., and Giu-Ching Ting: J. Pharmacol. & Exper. Therap. **18**: 373, 1921.

bronchial wall. Fraenkel [2] denied the concept of an ectatic dorsal wall of the trachea, which was advanced on the basis of casts.

Rabbits were given injections of india ink in the manner described. The lungs were fixed in solution of formaldehye U.S.P. without opening the trachea and were then embedded in toto in gelatin in order to avoid the artefacts of shrinkage attendant on pyroxylin and paraffin embedding. Frozen sections were cut at the levels of the trachea and carina and at the ostia of secondary bronchi. These showed that the india ink proceeds by way of the external lateral grooves into the lateral and dorsal branches of both main bronchi and so on at each branching (fig. 4). This lateral shunt insures the development of a transverse band area in the lower portion of the upper lobes and the upper portions of the lower lobes.

The mechanism of development of the transverse band lesion when the animal is in the supine position is somewhat different. A dorsal view of a rabbit's tracheobronchial tree demonstrates that the ostia of the aforementioned secondary bronchi lie chiefly in the ventral aspect. Thus, when the animal is in the supine position, they must act as vent holes of the main bronchus, carrying particulate or fluid matter into the transverse band area.

At autopsy the transverse band area in man cannot be clearly demonstrated unless solution of formaldehyde is injected into the organ intratracheally or by way of the pulmonary artery. After fixation, the lungs are sectioned coronally. In some cases it is possible to see or even feel the band lesion in the uncut lung. Although no such observations on man as described here have hitherto been published, experimental workers have apparently observed the predilection of particulate matter for the transverse band area. Austrian and Willis [3] noted that on infecting rabbits with tubercle bacilli by the tracheal route, the lesions appeared preponderantly in the upper parts of the lungs. Soper, Sampson and Haskins [4] observed the same result when using the nasal route. As has been mentioned, the transverse band area is observed not only in tuberculosis but also in pneumonoconiosis (fig. 5). This was substantiated by Dressen and Jones,[5] who said: "The coalescing nodules on becoming confluent . . . tend to be predominantly subapical in location." And again they found that "the anthracosilicotic lung is characterized pathologically by a silicotic fibrosis . . . in the infraclavicular regions of the lung."

2. Fraenkel, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen **21**:267, 1913.

3. Austrian, C. H., and Willis, H. S.: Am. Rev. Tuberc. **14**:306, 1926.

4. Soper, W. B.; Sampson, H. C., and Haskins, C. H.: Am. Rev. Tuberc. **15**:88, 1927.

5. Dressen, W. C., and Jones, R. R.: J. A. M. A. **107**:1179, 1936.

The involvement of the transverse band area has also been observed at autopsy in cases of "lipoid" pneumonia and in cases of hemorrhage into the respiratory tract.

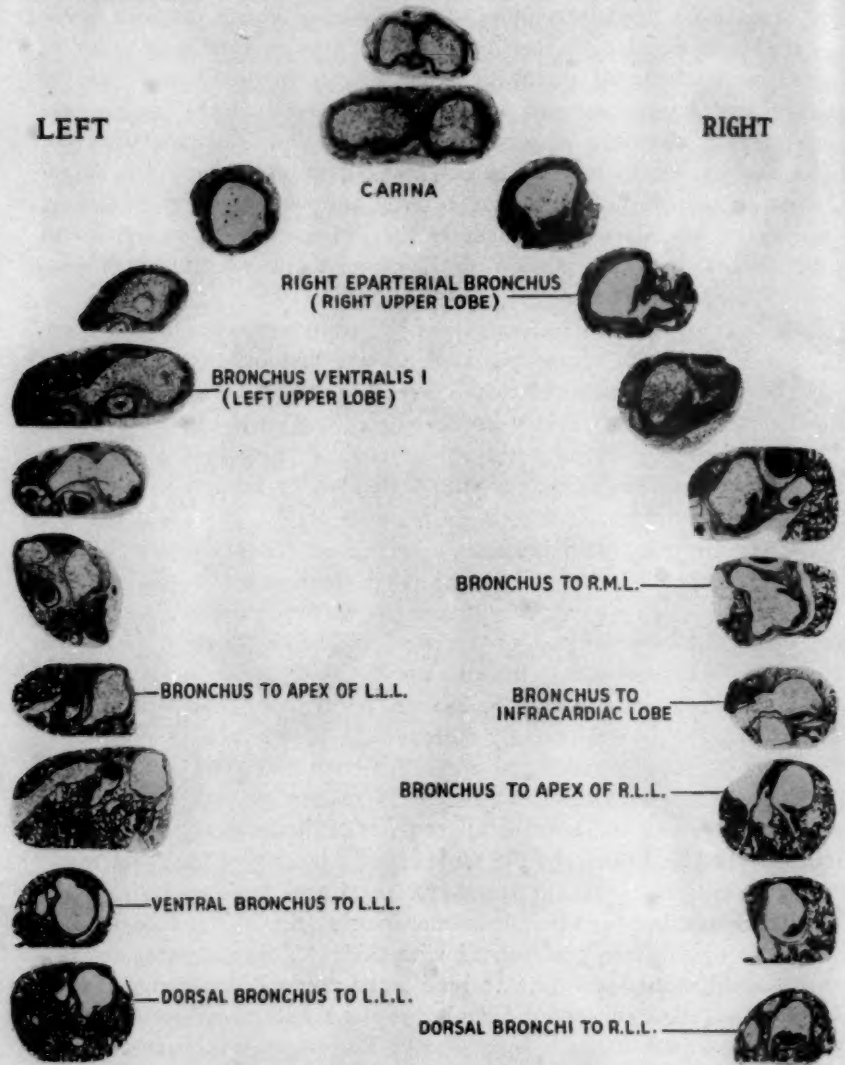

Fig. 4.—Serial sections of a rabbit's trachea and main bronchi, sectioned after aspiration of india ink, demonstrating lateral flow. *L. L. L.* signifies left lower lobe; *R. M. L.*, right middle lobe; *R. L. L.*, right lower lobe.

The mechanism in question holds only for fluids or particulate matter suspended in fluid. Particulate matter suspended in air is not influenced by the architecture of the tracheobronchial wall. It shows axial flow in the column of respired air and is distributed in a uniform

fashion to all parts of the lung. This was demonstrated by keeping guinea pigs in an atmosphere laden with charcoal dust. The lungs of animals killed soon after cessation of the aspiration of dust showed diffuse pigmentation of the lungs. At first sight this observation appears

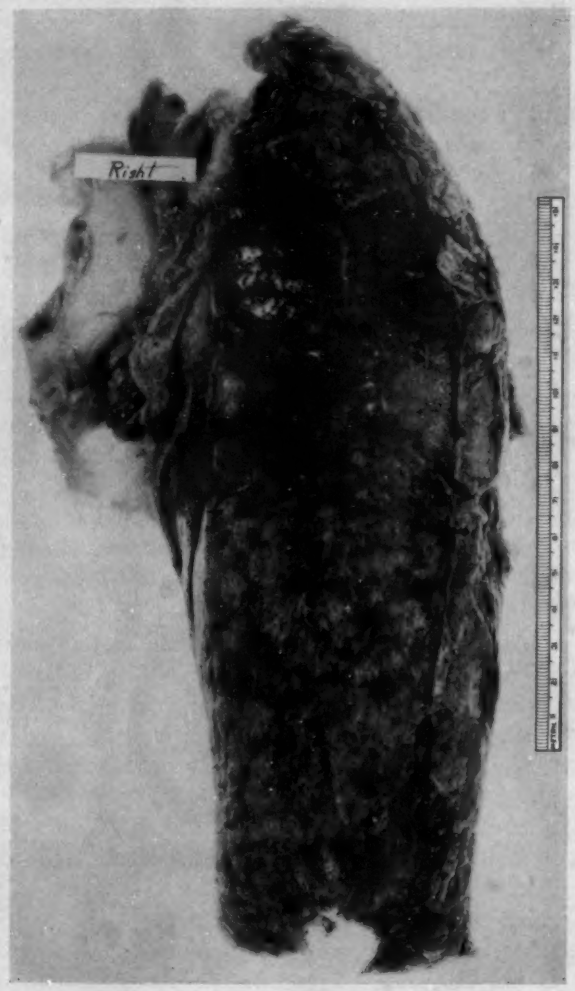

Fig. 5.—Transverse band lesion in pneumonoconiosis.

to contradict the observations made in cases of pneumonoconiosis. Nevertheless, the lesions seen in this disease are only indirectly the results of aerogenous transmission of dust. After the inhalation of the particulate matter the physiologic removal of the dust must lead, in part, to fixation and concentration of the particulate matter in the lymphatics and lymph nodes. Some of the dust, however, remains in the air pas-

sages and, becoming caught in the mucus of the bronchial wall, is started on its way to the trachea by the cilia and the peristalsis of the bronchial musculature. In the latter instance the particulate matter is suspended in a fluid medium and is governed by the law of lateral flow which has been outlined. In this way, particulate matter at first aspirated and distributed uniformly is finally concentrated in the transverse band area. Experiments to test this hypothesis further are now in progress.

The concept of the transverse band area may also be applied in the field of pulmonary abscess. The fact that (Freedlander [6]) "the great majority of solitary lung abscesses localize in a relatively small area, comprising the apex of the lower lobe posteriorly and the posterior tongue of the upper lobe," i. e., the transverse band area, lends support to the view that these abscesses result from aspiration of infected material.

The problem of apical tuberculosis, the characteristic form of adult, or reinfection, pulmonary tuberculosis, may also be attacked from this point of view. It is a common observation at the autopsy table that the oldest location of apical tuberculosis is the dorsovertebral portion of the upper lobe and that from here the disease extends caudally and in a spiral fashion toward the axilla and mediastinum. This area is supplied by a bronchus which is the most lateral tributary of the main primary bronchus and is hence frequently invaded because of the mechanism of lateral flow developed above. It is therefore quite possible that apical tuberculosis may owe its prevalence in part to the lateral flow mechanism of transportation of particulate matter suspended in fluid. This would be additional evidence in favor of an exogenous origin of the infecting organisms in adult tuberculosis, but this subject is far too complex to be explained by any one factor.

SUMMARY

A distribution of inflammatory lesions of the lungs in the lower third of the upper lobe and the apex of the lower lobe on the right and, on the left, in the middle third of the upper lobe and the apex of the lower lobe is described. Predominant involvement of this portion of the lungs, named herein the transverse band area, was found in man in tuberculosis, pneumonoconiosis, aspiration of blood, "lipoid" pneumonia and pulmonary abscess, conditions which are generally conceded to be accompanied by bronchiogenic distribution. The distribution of india ink to analogous areas can be demonstrated in rabbits and guinea pigs by intratracheal injection of the ink into the living animal. The mechanism of lateral shunt involved in this phenomenon is ascribed to the contour of the tracheobronchial wall and obtains only in the case of fluid or particulate matter in suspension.

6. Freedlander, S. O.: Ohio State M. J. **32**:832, 1936.

CONGENITAL ANEURYSM OF THE MEMBRANOUS SEPTUM

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Congenital aneurysm of the membranous septum, although of little clinical importance, presents an interesting morphologic and embryologic abnormality. Recently the hearts of two mongolian idiots presenting this anomaly came to our attention. The relative infrequency with which this condition is reported and its questionable etiology warrant, we believe, a report on these hearts and an attempt at interpretation.

CASE 1

A girl aged 13 months was brought to the hospital with a complaint of periodic difficulty in breathing and cough of several months' duration. She was born at the seventh month of gestation. The Wassermann and Kahn tests of the parents' blood were negative. The child had the mongoloid facies and signs of bronchopneumonia but improved and was discharged after two weeks. She reentered the hospital several days later with marked dyspnea and cyanosis; occasional crepitant râles were heard throughout both lungs posteriorly; but the heart appeared normal. The temperature was 104.4 F. Death occurred after two days.

Postmortem Examination.—Aside from the observations on the heart, the pathologic diagnosis was: acute purulent tracheobronchitis, bilateral confluent bronchopneumonia, cloudy swelling of the liver and kidneys and acute splenic hyperplasia.

Heart (figs. 1, 2 and 3): The heart was normal in size and shape. From the base, two arterial vessels of about equal size emerged, one anterior and to the left, the other posterior and to the right. The apex was formed by the left and right ventricles. The various chambers of the heart were in their normal relationships.

The superior and the inferior vena cava and the coronary sinus entered the right auricle normally. The eustachian and thebesian valves were normal. The limbus (septum secundum), although well formed, described a broad arc, measuring 1.7 cm. in the horizontal and 1.2 cm. in the vertical diameter. The septum primum in its postero-inferior portion presented two oval deficiencies in continuity, measuring 1 and 2 mm. in diameter, respectively. The free edge of the septum was directed anteriorly and superiorly. Projecting from the middle of this free edge, two bands with minute lacelike interdigitations ascended superiorly

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From the Department of Pathology, Nelson Morris Institute for Medical Research, Michael Reese Hospital.

EXPLANATION OF FIGURES 1 TO 6

Fig. 1 (case 1).—Right ventricular and auricular view: *TV* indicates the tricuspid valve; *A*, the aneurysm. The aneurysm bulges and displaces the medial leaflet of the tricuspid valve.

Fig. 2 (case 1).—Right ventricular view, taken from the inferior aspect of the heart, looking toward the infundibulum: *TSM* indicates the trabecula septomarginalis; *CS*, the crista supraventricularis; *SMB*, the septal muscle bundle; *PMB*, the parietal muscle bundle.

Fig. 3. (case 1).—Left ventricular view: *Ao* indicates the aorta; *A*, the aneurysm; *SV*, the ventricular septum. Note the displaced aorta, at the base of which lies the aneurysm.

Fig. 4 (case 2).—Right ventricular and auricular view: *A* indicates the aneurysm; *TV*, the tricuspid valve; *L*, the limbus; *SP*, the septum primum. The aneurysm bulges into the medial leaflet of the tricuspid valve.

Fig. 5 (case 2).—Infundibular view of the right ventricle: *TSM* indicates the trabecula septomarginalis; *CS*, the crista supraventricularis; *SMB*, the septal muscle bundle; *PMB*, the parietal muscle bundle.

Fig. 6 (case 2).—Left ventricular view: *A* indicates the aneurysm; *AO*, the aorta; *SV*, the septum ventriculorum. Note the displaced aorta riding over the aneurysm of the pars membranacea.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Figures 1 to 6

and anteriorly into the wall of the left auricle. The septum primum and septum secundum were anatomically united, but they left a longitudinally oval foramen ovale 1.3 by 0.8 cm., bridged by the inferior of the previously described bands. Thus there were three openings in the combined septum: the foramen ovale and the two small openings in its postero-inferior part. The endocardium about these openings was markedly thickened on the left auricular aspect of the septum and less so on the right auricular aspect.

The inferior leaflet of the tricuspid valve and the corresponding papillary muscles presented no abnormality. On the line of closure of the lower two thirds of the medial leaflet there was a small pinpoint-sized excrescence. Two similar excrescences were present on the anterior leaflet. Aside from these outgrowths, these portions of the valve and their corresponding papillary muscles presented no abnormality. Projecting into the upper third of the medial leaflet was a roughly circular pouch, 1.2 cm. in its horizontal and 1.4 cm. in its largest vertical diameter, which was thin walled and in a few areas transparent. On its anterior two thirds were seen the base and distal portion of the affected leaflet. It is thus evident that the posterior third of the pouch projected into the right auricle and that the base of the upper third of the medial leaflet was centrally protuberant from the circular rim of the tricuspid orifice. From this portion of the valve a few small endocardial bands extended to the adjacent endocardium of the ventricle. The right auricular and ventricular aspect of the pouch was smooth and glistening.

The right ventricular cavity was of normal size and shape, and its wall measured 1.5 mm. in thickness. The muscle bundles of the right ventricle presented the following topography (fig. 2): Commencing in the upper left margin of the right ventricle a small but thick muscle bundle bridged the left upper portion of the ventricular cavity to insert on the septum. It then continued its ascent for about 0.5 cm. to insert at the base of the left half of the septal cusp. A second small round thick muscle bundle originated at the origin of the anterior papillary muscle. This was apparently the trabecula septomarginalis, which bridged the left midlateral portion of the ventricular cavity to reach the septum. Here it united with a wide thick muscle bundle which originated at the midportion of the left margin of the ventricular septum. This was apparently the septal muscle bundle (septal portion of the crista supraventricularis) (described later) which obliquely ascended the septum toward the right. It inserted at the base of the right half of the septal cusp of the pulmonary valve. It imperceptibly fused with a small parietal muscle to form an arch over the base of the ventricular cavity. The parietal muscle bundle shortly terminated 0.5 cm. below the right posterior cusp. From the inferior border of the arch a large and a small muscle bundle descended on the anterior wall of the right ventricle. Small columnae carneae also descended from the base of the right posterior and anterior cusps of the pulmonic valve. The pulmonary artery emerged normally from the right ventricle, and its orifice and valve were normal. The ductus arteriosus was closed.

The left auricle received the four pulmonary veins normally. The mitral orifice, valve and corresponding papillary muscles were normal.

The left ventricular cavity was of normal shape and size, and its wall measured 0.3 cm. in thickness. The complete extent of the membranous portion of the interventricular septum was outpouched toward the right ventricle in the form of a saccular diverticulum with a half triangular, half circular orifice. The right anterior and posterior aortic cusps formed its upper steeple-shaped margin, while the upwardly concave muscular septum made up its lower boundary. The endo-

cardium about the lower and posterior margins was thickened, white and glistening. The inner lining of the walls and fundic portion of the pouch was likewise smooth and glistening. The direction of the muscular ventricular septum was such that its plane was directed toward the anterior right portion of the lumen of the aorta. The aorta emerged from the left ventricle in a somewhat slanting form so that the right sinus of Valsalva was on a lower level than the posterior. The coronary arteries arose high in the sinus of Valsalva, but otherwise their mouths and courses were normal. The large vessels were given off normally. The condition of the heart may be summarized as: congenital aneurysm of the mem-

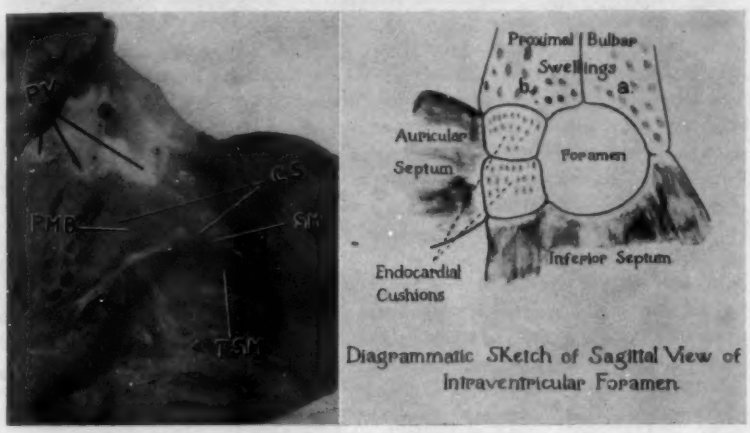

Fig. 7

Fig. 8

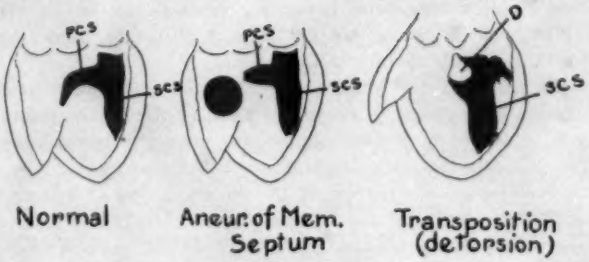

Fig. 9

Fig. 7.—Normal topography of the muscle bundles of the right ventricle: *CS* indicates the crista supraventricularis: *TSM*, the trabecula septomarginalis; *PV*, the pulmonic valve; *SMB*, the septal muscle bundle; *PMB*, the parietal muscle bundle.

Fig. 8.—Schematic diagram of the formation of the pars membranacea.

Fig. 9.—Comparative study of muscle bundles. *PCS* indicates the parietal portion of the crista supraventricularis (parietal muscle bundle); *SCS*, the septal portion of the crista supraventricularis (septal muscle bundle); *D*, the defect of the ventricular septum.

branous septum, bulging into the right ventricle and auricle and displacing the base of the upper portion of the medial tricuspid leaflet; fenestration of the septum primum, and patent foramen ovale.

CASE 2

A boy aged 5 months was brought to the hospital dead. Little is known of the previous history except that the child had been ill with pneumonia for one week. Nothing concerning the birth or the parental history was available.

Postmortem Examination.—Aside from the observations on the heart, the pathologic diagnosis was: mongolism; multiply and incompletely lobulated left lung; atelectasis (bilateral); compensatory patchy bullous emphysema (bilateral); bronchopneumonia (lower lobe of right lung), and cloudy swelling of the liver and kidneys.

Heart (figs. 4, 5 and 6): The heart was horizontally oval, with a slight bulge in the anterosuperior aspect beneath the pulmonary artery. The apex was formed by the left and right ventricles. From the base two vessels of about equal size emerged, one anterior and to the left, the other posterior and to the right. The relationship of the various chambers was normal.

The superior and the inferior vena cava and the coronary sinus entered the right auricle normally. The mouth of the coronary sinus was very wide, measuring 1 by 0.5 cm. in its greatest diameters. The eustachian valve was rather small, and its left margin was adherent to a strong band of tissue which formed the right superior rim of the coronary sinus. Bridging the lumen of the mouth of the sinus there was a thin strand of tissue, evidently the remains of the thebesian valve.

The limbus was well formed but described a very wide arc, which bordered a widely patent foramen ovale, measuring 2.3 by 2 cm. in its greatest dimensions. The septum primum, which was fused with the limbus (septum secundum), was markedly fenestrated where it faced the foramen ovale, and its free edge pointed anteriorly and slightly superiorly. Thus the foramen ovale was practically completely patent. The endocardium bordering the foramen on its right auricular aspect was thickened and white, but smooth and glistening, while that of the left auricular aspect was only slightly thickened.

The anterior and inferior leaflets of the tricuspid valve and their corresponding papillary muscles were normal. The upper third of the medial leaflet appeared to be replaced by a saclike structure bulging into the right ventricle and measuring 0.8 by 0.7 by 0.2 cm. Its right ventricular aspect was covered by valve tissue, evidently the remains of this portion of the tricuspid. No chordae tendineae were connected with this portion of the affected valve. The pouch was lobulated, and its right ventricular aspect was smooth and glistening. The endocardium of its auricular boundary was markedly thickened and white, but smooth and glistening.

The right ventricular cavity was of normal size and shape. Its wall measured 0.2 cm. in thickness. The trabecula septomarginalis bridged the ventricular cavity to join a septal muscle bundle. The latter obliquely ascended the septum, terminating at the base of the septal cusp of the pulmonic valve. A second muscle bundle lay beneath the bundle just described. Either or both of these muscle bundles corresponded to the septal muscle bundle (septal portion of the crista supraventricularis). Between the two muscle bundles there was a shallow trough-like separation which terminated superiorly at the junction of the septal and right posterior cusp of the pulmonic valve. At its termination it was in close proximity on its right side to a nichelike formation. The inferior component of the septal muscle bundle fused with the parietal muscle bundle, situated on the antero-

superior wall of the right ventricle (thus forming the arch). The parietal muscle bundle terminated rather abruptly, a little below the right posterior cusp of the pulmonic valve. The latter thus failed to make its more usual further excursion along the anterior wall of the right ventricle. Instead, hypertrophied columnae carneae descended from the anterior cusp to terminate at the base of the anterior papillary muscle. The pulmonary artery emerged from the right ventricle normally, and its valve was of a normal configuration. The ductus arteriosus was closed.

The left auricle received the pulmonary veins normally. Its cavity was of normal size. The mitral valve and the corresponding papillary muscles were normal.

The wall of the left ventricle measured 2 mm. in thickness. Its lumen was of normal size and shape. The muscular portion of the ventricular septum in its ascent toward the aorta was so directed that its plane passed through the middle of the lumen of the vessel. The plane of the membranous septum met that of the muscular septum at an angle of about 120 degrees. The anterior part of the membranous septum bulged outward into the right ventricle in the form of a diverticulum, which produced the saclike projection in that ventricle which has been described. The dimensions of its roughly oval-shaped mouth were 0.8 by 0.6 cm. Its fundic portion presented a few trabeculae, but its lining was smooth and glistening.

The aorta arose from the left ventricle, but in its emergence from the ventricle it straddled the muscular septum. Both coronary arteries arose at the upper limits of the sinuses of Valsalva. The coronary distribution, however, was normal. The innominate, left subclavian and left common carotid arteries were given off normally.

The condition of the heart is diagnosed as: congenital aneurysm of the membranous septum; fenestrations of the septum primum; patent foramen ovale; abnormally large ostium of the coronary sinus; defective formation of the thebesian valve, and right ventricular hypertrophy.

THEORIES AS TO ETIOLOGY

Thurnam intimated but Reinhard first definitely suggested that the abnormality might be of congenital origin. However, most of the early authors, including Pelvet, considered aneurysm of the membranous septum to be the result of endocarditis. Legg (1884) showed that there was a purely congenital type and differentiated it from an assumed endocarditic variety. Rokitansky believed that there were three factors in the production of aneurysm of the membranous septum: (1) congenital malformation of the membranous septum, (2) left intraventricular pressure and (3) inflammation. He did not state whether inflammation alone could produce an aneurysm of the membranous septum. Hart accepted the first two factors of Rokitansky but did not believe that inflammation could by itself produce such an aneurysm. Mall (1912) first demonstrated the abnormal direction of the muscular ventricular septum in its relationship to the aorta in these cases, and advanced the theory that aneurysm of the membranous septum is due to an insufficient shifting of the ventricular septum to the right and of

the aorta to the left. He thus considered the aneurysm congenital in all cases. Since then only Cannell and Massig have confirmed the anatomic findings of Mall. No other authors have mentioned any abnormality in the position of the ventricular septum.

Because of this obvious confusion in the literature as to the etiology of aneurysm of the membranous septum, we deemed it necessary to revaluate the theories from the standpoint of a large collection of instances in the literature.

Since the case described by Laennec [1] in 1826, about seventy cases of aneurysm of the membranous septum have been reported in the literature.

The theories which have been presented for the etiology of aneurysm of the membranous septum have in view the following possible causes:

1. Endocarditis (Pereira; Pelvet; Bouillaud; Dianoux; Féréol; von Buhl; von Krzywicki).

2. Endocarditis, with left intraventricular pressure due to obstruction of the aortic orifice (Peacock [1851] and others).

3. Friction of pendulous vegetations (Kidd [case 2]; West; Moxon; Ponfick).

4. Abnormal size of the membranous septum and pressure (Hart).

5. Abnormal size of the membranous septum, left intraventricular pressure and inflammation (?) (Rokitansky).

6. Thickening and shortening of the tricuspid valve with left intraventricular pressure (Zahn).

7. Atheromatosis (Todd; Klein; Plaisant; MacCallum).

8. Congenital maldevelopment (Reinhard; Tüngel; Hare; Legg [1884]; Irvine; Kidd; Taylor; Mall [1912a]; Apert; van Rijssel; Mencarelli [1929, 1930, 1934]; Eakin and Abbott; Cannell; Massig).

Endocarditis.—That there are cases of aneurysm of the membranous septum in which no signs of old or recent endocarditis are present was conclusively demonstrated by Reinhard, Tüngel and Hare; it was emphasized by Legg (1884) and confirmed by succeeding authors. Certainly in such cases there is no reason to assume an inflammatory origin. On the other hand, it has not been proved that endocarditis alone can produce an aneurysm involving only the membranous septum, although this possibility has been freely stated and quoted in the litera-

1. The authors' reprints include a bibliography. In some instances more than one article by the same author is cited in the text. The article referred to is designated by the year of publication in parentheses, plus the letter a or b if the articles were published in the same year.

ture. That an ulcerative process may produce perforation of the membranous septum is common knowledge (Gutzeit; Youmans). On this basis one may *a priori* postulate that a more prolonged chronic process may result in weakening and resultant aneurysmal dilatation. However, it would be an extremely unlikely assumption that mural endocarditis could be present without valvular involvement. And even when there is histologic evidence of inflammation only in the membranous septum, it is difficult to exclude a primary malformation with its known susceptibility to secondary endocarditis.

Thus the postulates of Legg (1884) for a congenital and an assumed endocarditic type cannot be rigidly applied. An aneurysm may be congenital even though the membranous septum and even the aneurysm itself present endocarditis. Only in the cases of Caubet, Talamon, Quain, Wilson and Guccione, because of the extent of the inflammatory involvement, may the aneurysm be assumed to be endocarditic, though we are by no means certain that the endocarditis did not occur secondarily. Other cases in which endocarditis of the membranous septum was presented, however, are considered probable or possible instances of congenital aneurysm.

Intraventricular Pressure (Left Ventricle).—Increased left intraventricular pressure should not by itself be considered a cause of aneurysm of the membranous septum. In the first place, whereas left ventricular hypertrophy is an everyday pathologic occurrence, aneurysm of the membranous septum is relatively rare. Furthermore, in only seven cases in our series collected from the literature was isolated left ventricular hypertrophy recorded. In only four of these did it exist as a factor alone, without inflammation. In eight cases there was hypertrophy of both ventricles, so that the factor here was minimal. Further very strong evidence against the mechanical factor here was a group of six cases in which there was isolated right ventricular hypertrophy. Especially is this suggestive in the cases of Eakin and Abbott and in our own case 2. In the former case the right ventricle was more than twice the thickness of the left, and in ours it was of about equal size, and yet the aneurysm bulged to the right. Evidently in these cases the direction of the aneurysm must be accounted for by the peculiar location and direction of the aorta and the resultant local current relationships. Isolated hypertrophy of the left ventricle without a predisposing congenital abnormality of the septum is an incidental observation in the very few cases in which it is present.

Can an increase in left ventricular pressure after birth produce an aneurysm in a congenitally malformed septum membranaceum? Goehring could not conceive of such an aneurysm burrowing into the firm fibrous tricuspid ring. He thought that this could occur only dur-

ing the stage when the valve apparatus is of muscular consistency. However, the aneurysm does not burrow into the ring itself in all cases; in some it projects either anterior or posterior to it. When, as in our cases, the base of the valve is caused to protrude by the aneurysm and the valve structure is atrophied, one may consider the aneurysm as having occurred in utero.

Cases have been recorded in the literature in which there was stenosis of the aortic orifice with pendulous vegetations and left ventricular hypertrophy. The influence of friction, inflammation and pressure here is suggestive but conjectural.

Pull of an Adherent Tricuspid Leaflet.—In those few cases in which there is a thickened and adherent tricuspid leaflet, if the resultant traction is to be considered a factor, the line of traction should be on the outpouched portion of the septum by the thickened cusp. This seems to have been true in the cases observed by Merkel and Zahn but not in the case of Irvine. However, thickening of the tricuspid valve occurs without aneurysmal formation of the pars membranacea. Furthermore, because of the apparent rarity of a thickened tricuspid valve in aneurysm of the membranous septum (only three cases), we believe it is more logical to consider the observation coincidental.

Atheromatosis.—It is peculiar that in the cases mentioned in which the aneurysm was possibly due to atheromatosis, although this disease was shown in the aorta, no unusual changes were presented in the aortic valve. It seems that if the process extended down and into the septum, it should also involve the aortic valve. Furthermore, Klein admitted that there was no histologic evidence that could be interpreted as specifically characteristic of atheromatosis. Therefore, we do not believe that this factor warrants undue consideration.

Summary.—From the foregoing analysis, we may consider (1) congenital malformation of the septum and (2) inflammation, alone or with left ventricular hypertrophy, as possible factors in the etiology. Since we are unable to state at the present time whether inflammation alone can produce an aneurysm of the membranous septum, we have limited our study to the congenital variety. And accordingly we have classified cases as *definitely, probably* or *possibly* congenital, depending on the presence or absence of the inflammatory factor. Those cases in which no endocarditis was shown in any part of the heart are considered definitely congenital. Also some of the cases in which there was no evidence of recent or old inflammation of the aneurysm of the membranous septum or of the aortic valve but in which endocarditis of the mitral or tricuspid valve was present are likewise considered definitely congenital, although this is less certain than in the former

cases. Those cases, however, in which recent or old endocarditis of the aortic valve was present without left ventricular hypertrophy and without any change in the membranous septum or aneurysm are considered in the probable class. Those cases in which aortic endocarditis was present with left ventricular hypertrophy and without changes of the membranous septum or of the aneurysm are considered possibly congenital. Also a few cases are called possibly congenital notwithstanding that endocarditis was present in the membranous septum. In some cases, accessory congenital or endocarditic evidence has influenced the classification.[2]

EMBRYOLOGIC EXPLANATION OF CONGENITAL ANEURYSM OF THE MEMBRANOUS SEPTUM

An understanding of the underlying embryologic abnormality in congenital aneurysm of the membranous septum necessitates a brief description of the normal development of the septum.

This process occurs when the fetus is from 10 to 15 mm. in length. The formation of the pars membranacea is more or less intimately connected with the formation of the bulbar septum. The formation of the latter is accomplished by the fusion of bulbar swellings A and B, pursuing a tortuous course in the lumen of the aorta. According to Tandler, bulbar swelling A (fig. 8) becomes continuous with the anterior prolongation of the interventricular septum. Swelling B (fig. 8) deviates to the right and becomes broadened and flattened. The posterior part of the interventricular septum extends toward the right tubercle of the posterior endocardial cushion. The interventricular foramen is thus bounded by a spirally directed ridge composed of the free concave border of the proximal septum bulbi superiorly and anteriorly, the interventricular septum anteriorly and inferiorly and the right tubercles of the anterior and posterior endocardial cushion posteriorly. In describing the closure of this foramen and the formation of the membranous septum, Tandler was somewhat noncommittal, stating that the bulbar septum meets the inferior septum, the fused atrioventricular cushions contributing to a degree that cannot be estimated. Mall, who bounded the foramen practically as Tandler did but gave more extent to the endocardial cushions, was more definite as to its ultimate fate. This wide interventricular foramen is also the vestibule of the aorta. The pars membranacea, Mall believed, is formed by the left wing of the intermediate septum (the fused endocardial cushions) growing down to meet the inferior septum. Fraser likewise believed that the

2. The authors' reprints include a table presenting this classification of the cases, with the facts responsible for their grouping.

fused endocardial cushions form the membranous septum, the right end of the upper (anterior) cushion forming the auriculoventricular portion, and the whole extent of the lower (posterior) one forming the intraventricular portion. In his interpretation (and we believe one can infer the same from that of Mall) the "true" interventricular foramen is never closed, remaining the vestibule of the aorta. Pernkopf and Wirtinger likewise were of the opinion that the endocardial cushions form the pars membranacea.

These apparently divergent opinions are really not strongly contradictory. Since the bulbar septum and the inferior septum face each other at two different planes, what actually constitutes the interventricular foramen is a matter of interpretation. The oblique spirally bounded foramen described and believed closed by Tandler is in a different plane from the more vertically directed foramen of Fraser which remains as the vestibule of the aorta. And the similarly bounded foramen of Mall closed by the pars membranacea is only one aspect of the larger space which remains the vestibule of the aorta. The pars membranacea closes the foramen of Tandler, while it forms the right border and floor of the foramen of Fraser (the vestibule of the aorta). The essential discrepancy lies in the part played by the endocardial cushions and proximal bulbar swellings in the formation of the membranous septum. Whereas Tandler seemed to favor the bulbar swellings but was noncommittal, Mall and Fraser put the greatest responsibility on the endocardial cushions. Gunn and Dieckmann, in their interpretation of two congenital hearts of mongols with persistent foramen primum and foramen interventriculare, bring evidence in favor of the endocardial cushions. Spitzer, who originally derived the pars membranacea from the anterior endocardial cushion and the proximal bulbar swellings, has more recently determined its origin from the bulbo-auricular spur.

However, in order that the pars membranacea may develop as described, certain embryologic conditions must be satisfied. Mall (1912a) believed that the muscular septum must have moved sufficiently to the right and the aorta sufficiently to the left for the aortic vestibule, and hence the pars membranacea, to develop normally. Fraser showed that the direction of the bulbus, which is to the right of the right tubercles of the anterior and posterior endocardial cushions, must be shifted to the left so that its lumen is in line with the right ends of the cushions. According to this author, this is achieved only if the bulboventricular ridge disappears.

Here again these two points of view are not divergent but complementary. Both Mall and Fraser agreed that the proper position of

the aortic portion of the bulbus is an important prerequisite for the development of the pars membranacea. And Fraser further suggested that this position is dependent on the disappearance of the bulboventricular ridge.

It is thus evident that the factors which may theoretically produce abnormalities in the pars membranacea are: (1) defective formation of the endocardial cushions; (2) isolated defective fusion of the proximal bulbar swellings A and B with each other or with the endocardial cushions; (3) abnormal position of the proximal bulbar septum in relation to the muscular ventricular septum (which may be brought about by persistence of the bulboventricular ridge (Fraser).

As far as defective formation of the endocardial cushions is concerned, this should be strongly considered. It is well known that the congenitally defective hearts of mongols often exhibit a persistent foramen primum and foramen interventriculare. And, as Gunn and Dieckmann have shown, it is most logical to assume a defective formation and fusion of the endocardial cushions in these cases. One may, therefore, well postulate a similar inherent difficulty in our cases, resulting in a weakened septum with resultant aneurysmal dilatation. However, we have not found any similar case of aneurysm of the membranous septum in a mongolian idiot reported in the literature. Therefore, although the theory is suggestive in our cases, it would be presumptuous to project it as a generality without further evidence.

Defective fusion of bulbar swellings 1 and 3 has been advanced by Goehring as the cause of aneurysm of the sinus of Valsalva. The extent to which a similar primary lack of fusion of swellings A and B (not correlated with a shift in their position) may operate in the formation of an aneurysm of the membranous septum is of course a function of the participation of these swellings in the formation of the pars membranacea. In Tandler's version such a primary isolated defect must be considered. In the interpretation of Mall (1912b) and that of Fraser it is less likely to be a factor. There may likewise be a defective fusion of these swellings with the endocardial cushions. This is especially suggestive in cases in which the aneurysm is in the anterior part of the pars membranacea, as suggested to us by Abbott. The position of the bulbar swellings and the resultant bulbar septum must constitute a primary consideration in the formation of the anomaly, and hence this question more logically falls under our last theoretical possibility.

In the discussion of this last theoretical possibility, we are compelled to consider the abnormal position of the bulbar and muscular ventricular septums together, because in the case of their mutual malposition it would be difficult to decide which was the primary offender, and hence

Mall (1912a), who first advanced this theory, simply stated that the aorta is displaced to the right and the ventricular septum to the left.

The observations of Mall in cases of aneurysm of the membranous septum have been borne out by all those who have studied the direction of the membranous and muscular portions of the interventricular septum in this anomaly. Thus Cannell, Massig and we have found the aorta in the unusual position of somewhat facing both ventricles (figs. 3 and 6). And on looking at the illustrations of the specimens studied by Rokitansky and Eakin and Abbott we may make similar observations. In fact, Eakin and Abbott considered their case one of transposition. Therefore, of all the possibilities advanced in the foregoing paragraphs, the theory of Mall is the one best substantiated by definite anatomic evidence.

Of course, as suggested to us by Abbott, there may be cases in which there is no abnormality in the direction of the muscular ventricular septum. It is in these cases that a primary lack of proper fusion of A and B with each other or with the endocardial cushions must be postulated. Up to the present time, however, no report of a case has appeared in which it has been stated that there was absence of the abnormal direction of the ventricular septum when this has been looked for. And when we do find this abnormality, this seems to us to be the underlying fault.

Perhaps we may hazard a step further. Mall (1912a) made the interesting suggestion that if the process involved in the formation of the aneurysm was exaggerated, the aorta might have free communication with the right ventricle or arise from it and the interventricular foramen might remain open. In other words, the embryologic defect in the transposition of the arterial trunks and that in the formation of an aneurysm of the membranous septum may be conceived of as identical in type but differing in degree.

It is not within our province to consider at length the modern concepts of transposition. These we have dealt with in our article on transposition (1937). There we gave the reasons for disagreeing with Spitzer's mechanico-ontophylogenetic theory. We decided that transposition of the arterial trunks is due to an abnormality in the absorption of the bulbus as first postulated by Keith. This is brought about by an abnormality in the bulbo-auricular spur area. This produces increased back torsion in the proximal bulbar ostium, which results in lessened torsion of the distal bulbar ostium, which grossly gives the picture of transposition. Our study of the muscle bundles of the right ventricle in both normal and congenital hearts leads us to alter our nomenclature for these bundles. These we have named the parietal and septal muscle bundles (together forming the crista supraventricularis). We showed

that in various types of transposition the parietal muscle bundle (present on the anterior wall of the right ventricle) is shortened. The septal muscle bundle, however, often hypertrophies.

In our case 1, the parietal muscle bundle ends in the upper part of the anterior right ventricular wall (fig. 2). In case 2, the termination is still more abrupt, the muscle bundle ending in a nichelike formation, which externally produced a bulge on the anterior aspect of the base of the pulmonary artery (fig. 4). Normally the parietal muscle bundle should continue downward on the anterior wall of the right ventricle, terminating at the base of the anterior papillary muscle or some distance above it (figs. 7 and 9). In its course it is in close relationship with the base of the anterior leaflet of the tricuspid valve. The abrupt termination of this bundle in our cases, we believe, constitutes evidence in favor of transposition. The position of the aorta, practically straddling the ventricular septum, is further confirmatory. It practically constitutes a *reitende* aorta without the patent interventricular foramen. In the case observed by Eakin and Abbott, this was even more marked, and the abnormality was called by the authors a frank transposition, although the aorta arose from the left ventricle. The position of the aortic cusps, however, in our cases does not show any evidence of transposition.

Therefore, perhaps we may consider, as first implied by Mall (1912b), that aneurysm of the membranous septum is a mild form of transposition. The concomitant malformed aortic vestibule leads to the formation of an aneurysm in the pars membranacea.

Interesting in this respect are the associated abnormalities observed in the cases of aneurysm of the membranous septum reported in the literature. The case of Zadoc-Kahn and Cousin showed complete absence of the interauricular septum, while Tüngel's case and Reinhard's third case showed a defect in the lower part of this septum. These anomalies, of course, may be explained as due to local defective development of the septum primum and in the first case (Zadoc-Kahn and Cousin) also of the septum secundum. However, we may explain them, as well as those in our own two cases, as frequent concomitants of transposition. As far as anomalies in the aortic valve are concerned, Peacock's case showed an undivided aortic double cusp, and the cases of Zahn (case 1), Kidd (case 4) and Cannell (case 2) showed a bicuspid pulmonary valve with a rudimentary third cusp, while Reinhard's first case presented a fenestrated pulmonic valve. These anomalies may all be explained as localized defects in the formation of the distal bulbar swellings as in aneurysm of the sinus of Valsalva (Goehring). But here again inherent defects in the bulbar swellings are often correlated with abnormalites in their position which manifest

themselves by some form of transposition. Evidence in that direction may be cited in the tetrology of Fallot with a bicuspid pulmonary valve, truncus communis and truncus solitarius aorticus or pulmonalis with some form of transposition (Spitzer; Abbott; Humphreys; Shapiro).

The abnormality of the thebesian valve in our case 2 and of the eustachian valve as well in the case of Eakin and Abbott may be explained as a local abnormal formation of the right valve of the sinus venosus or as abnormal division of this valve by the sinus septum. In our case 2 the unusually strong sinus septum and wide mouth of the coronary sinus speak for the latter.

The high origin of the coronary arteries in the sinuses of Valsalva noticed by Reinhard, Cannell, Rae and ourselves may be explained either on the basis of downward pull of the valve cusps by the aneurysm (Reinhard) or as in some hypothetical way correlated with the abnormal position of the base of the aorta.

There remains to be considered a group of cases presenting either (*a*) a solitary aneurysm opening into both the aorta and the membranous septum (Hope, four cases; Todd; Peacock [1851]); (*b*) two separate aneurysms, one of the aortic sinus of Valvalva and the other of the membranous septum (Rogers; Kidd; Port) or (*c*) an aneurysm of the aortic valve and of the membranous septum (Dianoux; Tate; Weiss). If they are not simply coincidental, these anomalies may be due to a slight abnormality in the position of the proximal and distal cushions. This results distally in faulty union, as explained by Goehring, and proximally in malposition of the aortic septum. To what extent there may be faulty fusion proximally due to malposition of the swellings, resulting in the aneurysm of the membranous septum, as already discussed, is purely conjectural. In Tandler's and Spitzer's interpretation of the formation of the normal pars membranacea, this might be an outcome of the abnormal position and thus complete the picture. In the interpretations of Mall (1912b) and Fraser, since the endocardial cushions are the predominant if not the sole contributors in the pars membranacea, it is the *position* of the bulbar septum which is the predisposing factor in the formation of an abnormal pars membranacea, resulting in an aneurysm.

SUMMARY

We have presented two cases of aneurysm of the membranous septum. From a critical review of the literature we have shown that in most cases (our two cases included) aneurysm of the membranous septum is congenital. In explanation of the underlying embryologic fault in this anomaly, we have considered the following embryologic variants as possibilities: (1) abnormal formation and fusion of the

endocardial cushions, (2) abnormal formation and fusion of the bulbar cushions and (3) abnormal position of the proximal bulbar septum in relation to the muscular ventricular septum (which may be brought about by persistence of the bulboventricular ridge). From the analysis of our cases and those of the literature, we believe that the embryologic explanation most satisfactory for many cases of this anomaly is the theory of Mall (1912b), postulating an abnormal direction of the ventricular and bulbar septums. In our study of the muscle bundles of the right ventricle, we have further shown that the parietal muscle bundle is abnormally small in our cases of aneurysm of the membranous septum. This combined with the abnormal position of the aorta has led us to amplify the theory of Mall (1912b). We consider that in many cases congenital aneurysm of the membranous septum is a mild form of transposition. The concomitant of transposition, as we have previously postulated, is a malformation of the aortic vestibule, which in a mild form may present itself as an aneurysm of the pars membranacea.

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LYMPHADENOID GOITER

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Williamson and Pearse [1] in 1925 described a type of chronic thyroid disease characterized by lymphocytic infiltration and ending in myxedema to which they gave the name "lymphadenoid goiter." A year later, McCarrison [2] claimed to have produced the same type of goiter in white rats by feeding them a diet from which green vegetables and fruit were excluded.

The causes, histogenesis and clinical significance of this form of goiter are little understood. Most writers agree that the disease described by Williamson and Pearse is the same form of thyroid enlargement which Hashimoto [3] in 1912 designated struma lymphomatosa. There is, however, no agreement that lymphadenoid goiter represents a pathologic and clinical entity. Wegelin,[4] de Josselin de Jong,[5] Hertzler,[6] Jaffé [7] and others regarded it as an unspecific thyroiditis, while Williamson and Pearse denied that it was of inflammatory nature and expressed the belief that it represents a functional disorder leading to fibrosis of the thyroid. Hashimoto, Graham and McCullagh,[8] Joll [9] and de Quervain [10] contended that it is not a precursor of fibrosis or of Riedel's struma.

I had an opportunity to observe at St. Francis Hospital 4 cases corresponding in every detail with those reported by Hashimoto and Williamson and Pearse. My findings led to conclusions which are at variance with the view expressed by most writers. The cases are pre-

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sented because they suggest (1) that lymphadenoid goiter is a distinct pathologic and clinical entity and has no relation to Riedel's struma, (2) that it is not a true inflammatory process—not any more than so-called chronic cystic mastitis and (3) that the histologic changes characteristic of lymphadenoid goiter may be present in typical exophthalmic goiters. The last fact is of particular interest and has been overlooked by most writers.

REPORT OF CASES

CASE 1.—March 17, 1927, a white married woman aged 30 was admitted to the hospital with the history that she had noticed, three years before, enlargement of her neck. She took a "medicine for goiter" for a year. This diminished the size of the goiter somewhat. She had not taken any medicine for the past year and had been feeling well.

When young, she had measles and scarlet fever. Six years ago she had influenza. She had a child 11 years old, who was in good health. Her mother was operated on for goiter six years ago; the mother's goiter was apparently not toxic. The grandmother and three aunts had goiter. The patient began to menstruate at the age of 13. The flow was regular, normal in amount and without pain.

Examination.—She was a fairly well nourished white woman, weighing 121 pounds (55 Kg.) and measuring 64 inches (162.5 cm.) in height. There were no ocular signs suggestive of exophthalmic goiter. The thyroid was bilaterally enlarged; no nodules were felt. The heart appeared normal; the pulse rate was 80. The results of the examination of the chest and abdomen were negative. The urine had a specific gravity of 1.030 and an acid reaction; it showed no evidence of sugar but contained albumin (2 plus). The sediment contained many leukocytes. The white blood cell count was 5,200; the red blood cell count, 3,780,000. The hemoglobin was 59 per cent (Sahli). The basal metabolic rate was 6 per cent above normal.

Operation.—March 24, 1927, both lobes and the isthmus were resected under local anesthesia. The thyroid appeared about twice the normal size. It was of firm consistency, and there were few adhesions between the gland and the adjacent tissue. The operative wound was closed without drainage.

Postoperative Course.—The postoperative course was uneventful. There was no drainage from the wound. March 25, one day after the thyroidectomy, the temperature rose to 100.6 F.; the pulse rate, to 96. Both were normal three days later. The patient was discharged from the hospital April 3. The pulse rate at this time was 68.

Pathologic Report.—The removed tissue consisted of the right and left lobes and the isthmus. The weight was 45 Gm. The right and left lobes both measured 6 cm. vertically, 3 cm. transversely and 0.5 cm. anteroposteriorly. Both lobes had a normal contour, and there were no nodules. The capsule was thickened. The cut surface was uniform, firm, rubbery and white throughout. No colloid-filled follicles or nodules were recognized with the unaided eye.

Microscopic sections from various portions of the specimen showed regular interlobular septums. The fibrous tissue was not increased. The lobules were composed of small acini, measuring between 40 and 60 microns. Their form was round, oval or slitlike. The epithelium was high cuboid; on the average it was 12 microns high. There were no papillary projections into the lumens. Only few

of the acini were filled with red-stained colloid. Most of the acini were empty (fig. 1*A*). In several lumens groups of cells were found which looked like syncytium or giant cells. Some of the acini were lined with swollen, irregular cells having finely granular protoplasm, which stained intensively with eosin. The nuclei of these cells were of large size and stained almost black. There was diffuse

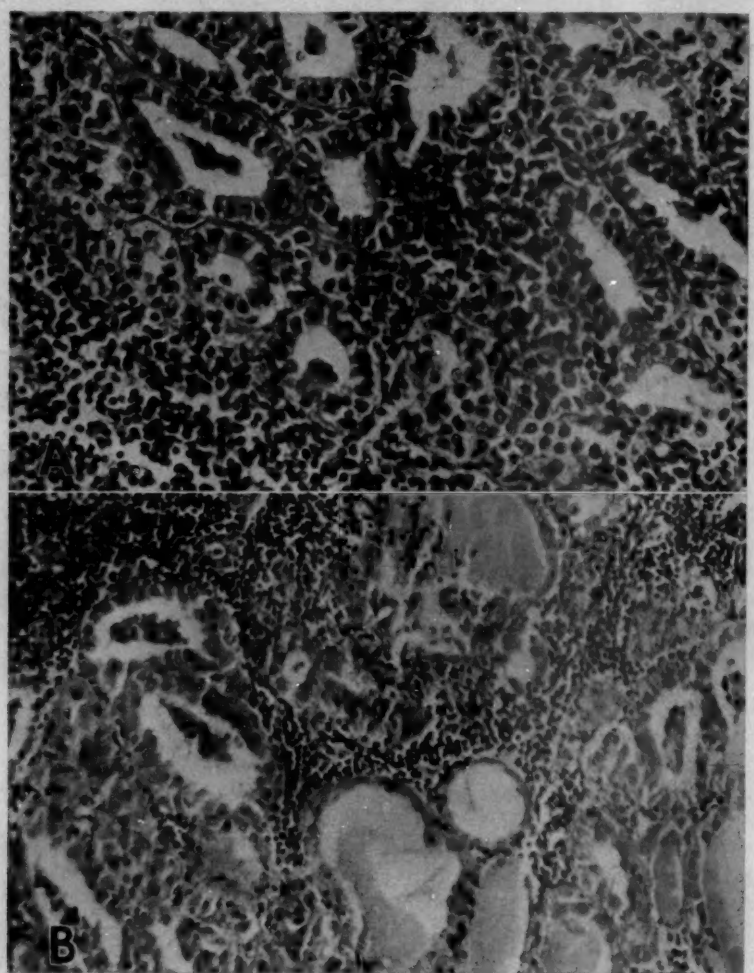

Fig. 1.—*A* and *B* are from portions of the same goiter removed nine years apart. In both specimens the characteristic changes are identical. There is no tendency of this goiter to develop into Riedel's struma. In *B*, many acinar cells are swollen and show pale red staining.

infiltration of the gland by lymphocytes, and there was an abundance of lymph follicles with large germinal centers.

Follow-up.—Several weeks after the operation, the patient showed severe symptoms of thyroid insufficiency. Her basal metabolic rate, June 6, was 45 per

cent below normal. She regularly took thyroid extract, which improved her condition markedly. The basal metabolism, which was determined every three months during the following years, averaged 10 per cent below normal.

The patient was readmitted to the hospital nine years after the first operation, i. e., Jan. 1, 1936.

History at Readmission.—In June 1935 the patient was frightened, and since then nervous symptoms had developed. She noticed, at the same time, enlargement of the left side of the neck. She had attacks of palpitation but felt more comfortable in the hot season. Her menstruation had been regular. During all the years following the first operation, the patient took thyroid extract. It was discontinued in June 1935.

Examination.—She was well nourished and weighed 132 pounds (59.9 Kg.). The pulse rate was between 68 and 74. There were no symptoms of myxedema. The isthmus and the left lobe of the thyroid were enlarged. The heart gave a slight soft blowing sound. The urine was negative in tests for albumin, sugar and blood. The basal metabolic rate was 4 per cent above normal.

Operation.—Jan. 10, 1936, the enlarged isthmus and left lobe were resected under local anesthesia. Dense adhesions were found adjacent to the thyroid. After the resection, the wound was closed without a drain.

Pathologic Report.—The specimen consisted of a thick isthmus and a large left lobe. It weighed 21 Gm. and measured 5 by 3 by 2.5 cm. The capsule was thickened, and the surface was finely lobulated. The cut surface was homogeneous, white and firm. No nodules were noticed. A small colloid cyst, measuring 3 by 6 mm., and several large follicles were recognized with the unaided eye.

Microscopically, the gland resembled closely the specimen removed nine years previously. There was the same abundance of lymphoid tissue, and many well formed lymph follicles with germinal centers were found throughout the sections. The only difference was the slightly larger amount of red-stained colloid in this gland (fig. 1 *B*). The diameters of most of the acini were between 50 and 80 microns. There were many empty slitlike lumens which contained cell groups. The epithelium varied in size. The height in most acini was from 9 to 12 microns. Many swollen granular cells staining bright red with eosin attained a height of from 18 to 21 microns. The connective tissue was not thicker in this specimen than it was in the first.

Case 2.—Dec. 30, 1935, a white woman aged 54 was admitted to St. Francis Hospital. She complained of a choking sensation and loss of weight. The following history was obtained:

She had lost about 30 pounds (13.6 Kg.) during the past year. She noticed that her neck enlarged. She did not become nervous, did not sweat unduly and suffered no change in appetite. Her heart did not produce any discomfort. She was married; she had no children.

Examination.—She was well nourished and did not appear sick. She had no ocular signs, and her hair was not dry. The heart was of normal size, and there were no murmurs. The chest and abdomen did not reveal pathologic changes. The pulse rate was 80. The urine was normal. Its sediment contained few leukocytes and few epithelial cells.

Operation.—Dec. 31, 1936, both lobes of the thyroid were resected under local anesthesia. Both lobes were found hard and symmetrically enlarged, with preservation of the normal contour. There were no adhesions between the lobes and the adjacent tissue. The wound was closed without drainage.

The postoperative convalescence was complicated the day after operation by muscle contractions. The temperature rose to 101.2 F. It returned to normal Jan. 6, 1937. The pulse rate was between 84 and 100 and returned to normal a few days later. The patient was dismissed from the hospital January 13. In March the basal metabolic rate was 15 per cent below normal. There were no definite clinical signs of myxedema.

Pathologic Report.—The two lobes of the thyroid weighed 34 Gm. Both lobes were enlarged, and the capsule was thickened. On sectioning, the cut surface was

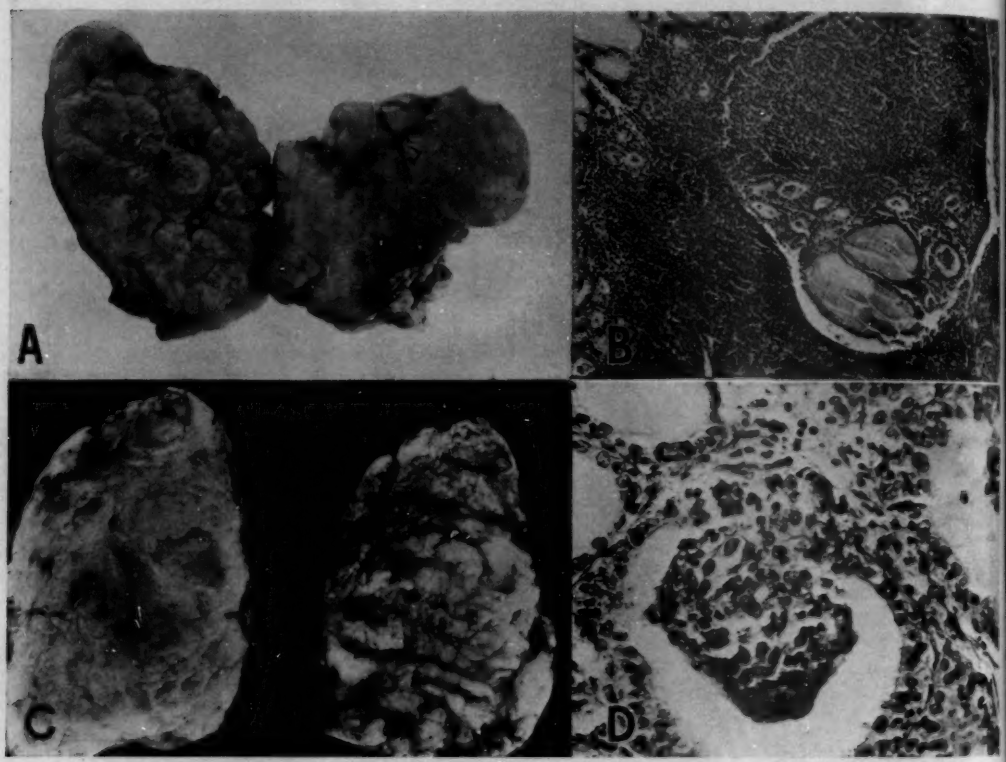

Fig. 2.—*A* and *B* represent case 2. The cut surface is dry and white. The photomicrograph shows an abundance of lymphoid tissue and characteristic epithelial changes. *C* is a lymphadenoid goiter from a 16 year old white girl. No colloid is recognized in the cut surface. *D* shows a bud of histiocytes protruding into the lumen of an acinus of *C*.

white, dry and uniform (fig. 2 *A*). Few large follicles were recognized. There were no circumscribed nodules.

Microscopic examination revealed distinct lobules. The connective tissue was not definitely increased. The most characteristic feature was the abundance of lymphoid tissue (fig. 2 *B*). Many large lymph follicles with germinal centers were found throughout the gland. Most acini were small, oval and narrow; they were without stained colloid. The average height of the epithelial wall was 13 microns. Several acini were lined with large pale-staining eosinophilic cells having

a diameter of about 20 microns. No mitotic figures were observed. While most of the acini measured about 40 to 60 microns in diameter, occasionally a larger acinus with columnar epithelium and well stained colloid was noticed.

CASE 3.—Sept. 4, 1936, a white girl 16 years old was admitted to the hospital. Her grandparents came from Switzerland. Four years ago, her mother noticed enlargement of the daughter's neck. The girl did not show any functional disturbance of the thyroid. She made good progress in school.

Examination.—She was a well developed, well nourished white girl 16 years old. A large thyroid, apparently nodular, was palpated. The chest and abdomen did not reveal pathologic changes. The urine had a specific gravity of 1.014, was clear and had a straw color. No albumin or sugar was found. The pulse rate was 80.

Operation.—September 5, the thyroid was resected. The right lobe was much larger than the left. The consistency was hard. There was not abundant bleeding. The surface of the thyroid was lobular. No adhesions were found between the gland and the surrounding tissue. The wound was closed without a drain.

The postoperative course was uncomplicated. After being dismissed from the hospital, the patient was advised to use iodized salt regularly. To the time of writing, no symptoms of myxedema have been recognizable. There has been no recurrence of the goiter.

Pathologic Report.—The resected tissue weighed 32 Gm. It consisted of the large right lobe, measuring 6 cm. vertically, 4 cm. transversely and 2 cm. anteroposteriorly. The three pieces removed from the left lobe measured 2.5 by 1.5 cm. The cut surface of the thyroid appeared homogeneous and white, and distinct septums were recognized. No colloid and no nodules were visible (fig. 2 *C*).

Microscopically, the tissue was divided into lobules by fibrous trabeculae of variable thickness. There was an abundance of lymphoid tissue, which was found diffusely in the septums and within the lobules. Numerous lymph follicles with large germinal centers were found throughout the gland. The acini were mostly of small size. The epithelial cells were cuboid. There were groups of red-staining pale cells of large size. Occasionally, multinucleated giant cells were present in the lumens. Most acini were without colloid. Few plasma cells were found in the interstitial tissue.

CASE 4.—An unmarried 29 year old white woman, a stenographer, was admitted to the hospital July 1, 1934. She was born in Texas. Her mother had goiter. Since puberty the patient had noticed pressure symptoms, such as tickling in the throat, a choking sensation and a feeling of fulness in the throat. During the past months these symptoms became more severe. During menstruation the patient noticed enlargement of the gland. She had never had any toxic symptoms, such as palpitation, loss of weight or increase of appetite. She had been more or less nervous all her life. Menstruation started at the age of 12 and was always regular.

Examination.—She was a well developed, well nourished white woman. There was no exophthalmos or other ocular sign. The tonsils had been removed. The lymph nodes of the neck seemed to be slightly enlarged but were not tender. The thyroid was large, hard, nodular. There was no pulsation or bruit. The heart was not enlarged, and there were no murmurs. The pulse rate was 68 and regular. The blood pressure was 98 systolic and 70 diastolic. The skin was fairly moist. There was a fine tremor of the hands. The urine was clear and the color of straw; the specific gravity was 1.008. The chemical and microscopic study of the urine revealed nothing pathologic.

Operation.—July 2, under local anesthesia, the muscles of the neck were separated, the goiter was dissected free, the upper and lower poles were ligated, and the thyroid gland was resected without difficulty. The wound was closed with one rubber drain.

After the thyroidectomy, there was never a rise in temperature or pulse rate, and the patient was dismissed July 10.

Several weeks after the operation, the patient began to have marked symptoms of myxedema. She took thyroid extract, and the symptoms of thyroid insufficiency disappeared promptly.

Pathologic Report.—The specimen weighed 31 Gm. The right lobe measured 4 by 3 by 2 cm.; the left, 4.3 by 2.5 by 2.8 cm. The cut surface was dry and whitish, and there were no visible acini.

Microscopic examination revealed small acini with an average diameter of 80 microns. The epithelial cells had diameters of from 6 to 12 microns. Many slitlike lumens contained groups of cells. The colloid was thin and often unstained; only occasionally red-stained colloid was noticed. The lymphoid tissue was abundant throughout the sections. The blood vessels were poorly filled with blood cells. The fibrous septums were thin.

COMMENT

The 4 patients were all females. While lymphadenoid goiter seems to be a disease chiefly of middle-aged women, 2 of the patients were in the second and third decade of life respectively. The observation of this disease in a 16 year old girl (case 3) does not support Graham's view that such goiter results probably from exhaustion atrophy of an exophthalmic goiter. Neither in this nor in any other of these cases could a history of antecedent hyperthyroidism be obtained. The first patient was operated on twice in an interval of nine years, and there was an occasion to study both surgical specimens. There was no difference in the microscopic structure of the goiter in the two specimens; in particular, no increase in fibrous tissue was noted in the second specimen as compared with the first. Therefore, the opinion of most writers that lymphadenoid goiter is a progressive disease ending in fibrosis (Riedel's struma) could not be substantiated. The findings suggest to the contrary that lymphadenoid goiter is neither the result of a burning-out of exophthalmic goiter nor a precursor of Riedel's struma but a distinct pathologic and clinical entity.

The pathologic features in these 4 cases were strikingly uniform. Grossly, there was diffuse bilateral enlargement of the thyroid. The weights of the resected specimens were between 30 and 45 Gm. Compared with the average weight of normal thyroids obtained at autopsy in this part of the country (23 Gm.), the weights of these thyroids were definitely increased. The contour of each of the glands was normal, and there were no firm adhesions to the surrounding structures. The cut surface was divided into lobules, and the structure was

uniform throughout the gland. The tissue was white, firm and hard. No nodules were visible.

The microscopic pictures in the 4 cases corresponded in every detail with the descriptions given by Hashimoto,[3] Williamson and Pearse [1] and Graham and McCullagh.[8] The most characteristic feature was the abundance of lymphoid tissue. Not only was the lymphocytic infiltration diffuse within the lobules and in the septums, but many lymph follicles with large germinal centers were present in every specimen. The acini were mostly of small size and had round, oval or, more often, slitlike lumens. The lining epithelium was high cuboid and measured between 8 and 12 microns. Stained colloid was extremely scanty and in most acini absent. Many lumens contained, in their centers, groups of cells which resembled giant cells or syncytium. The nature of these cells is not quite clear. Most writers describe them as desquamated epithelial cells. One sometimes sees, however, as in figure *2 D*, an acinus in which a bud of large mononuclear cells is protruding into the lumen through a defect in the epithelial lining. Such pictures suggest an origin of the intrafollicular cells from histiocytes. Lymphocytes and plasma cells are occasionally seen as well as these larger cells in the lumens.

There were other peculiar alterations of the epithelial cells, noticed in all cases. Some of the acinar cells were swollen and of irregular form. Their granular protoplasm took an intense stain with eosin, and the nuclei were also irregular in size and shape and stained deeply with hematoxylin. Usually one or two acini showed such a change in their epithelium (fig. *1 B*), or only few such cells were intercalated among others of the usual type in the acinar wall. Sometimes solid strands composed of pale red-staining cells were found surrounded by lymphocytes. These unusual cells have attracted the attention of previous writers, but there is no agreement about their significance. While Bruenger,[11] who described them in chronic thyroiditis, regarded them as showing regenerative or hypertrophic changes, Reist [12] contended that they are a sign of degeneration. Hertzler [13] ascribed to cells of this type a dysfunction responsible for myxedema and advised total thyroidectomy to eradicate such cell structures. In my opinion, these swollen eosinophilic epithelial cells resemble the pale red columnar duct cells which are so characteristic of chronic cystic mastitis. As in the latter disease, they are most likely metaplastic acinar cells the condition of which is due to chemical irritation.

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11. Bruenger, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:213, 1914.
12. Reist, A.: Frankfurt. Ztschr. f. Path. **28**:141, 1922.
13. Hertzler, A. E.: Surgical Pathology of the Thyroid Gland, Philadelphia, J. B. Lippincott Company, 1936, p. 198.

An increase in fibrous tissue, which is mentioned frequently as typical for lymphadenoid goiter, was missed in all my cases. As pointed out already, the two specimens removed from the same patient, nine years apart, did not differ in the amount of stroma.

The described histologic features must be regarded as responsible for thyroid insufficiency, so common in patients with lymphadenoid goiter. If this is true, it seems strange that identical histologic changes may be found in toxic goiters. Among the surgical specimens of this hospital, 23.3 per cent of the exophthalmic goiters showed small islands of dense tissue which were indistinguishable from lymphadenoid goiter. These areas were often visible with the unaided eye (fig. 3 *A*) and composed of the same small colloid-free acini, the same swollen pale epithelial cells and the same abundant lymphoid tissue as one finds in lymphadenoid goiter (fig. 3 *B* and *C*). Such areas were described by A. Kocher [14] in 1912 as exhausted lobules. Rienhoff [15] and Willer,[16] on the other hand, were of the opinion that such areas are hyperplastic foci which have not undergone involution after treatment with iodine as have the surrounding colloid-rich tissues. Broders [17] and Clute, Eckerson and Warren [18] regarded these foci as inflammatory owing to large doses of iodine. The last explanation is refuted by A. Kocher's experience that these islands are found as often in patients who have never received iodine. Pale red, enlarged cells were described in exophthalmic goiter by MacCallum [19] and Roussy.[20] Their significance was not clear to these observers.

Since it cannot be doubted that lymphadenoid goiter is associated with low function of the thyroid, the described dense areas in exophthalmic goiter can certainly not be regarded as hyperplastic, and the stand of A. Kocher that they are localized foci of exhaustion seems justified. The fact that they produce no clinical symptoms of myxedema is easily understood if one bears in mind that they are of limited extent as compared with the hyperplastic areas of exophthalmic goiter.

The similarity of the histologic pictures of lymphadenoid goiter and the small islands found in some exophthalmic goiters leads one to speculate on the histogenesis and function of these two forms of goiters, so dissimilar in their clinical symptoms.

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14. Kocher, A.: Virchows Arch. f. path. Anat. **208**:86, 1912.

15. Rienhoff, W. F., Jr., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 6, p. 73.

16. Willer, H.: Centralbl. f. allg. Path. u. path. Anat. **63**:337, 1935.

17. Broders, A. C.: Virginia M. Monthly **56**:453, 1929.

18. Clute, H. M.; Eckerson, E. B., and Warren, S.: Arch. Surg. **31**:419, 1935.

19. MacCallum, W. G.: J. A. M. A. **49**:1158, 1907.

20. Roussy, G.: Rep. Internat. Conf. Goiter (1933) **2**:175, 1935.

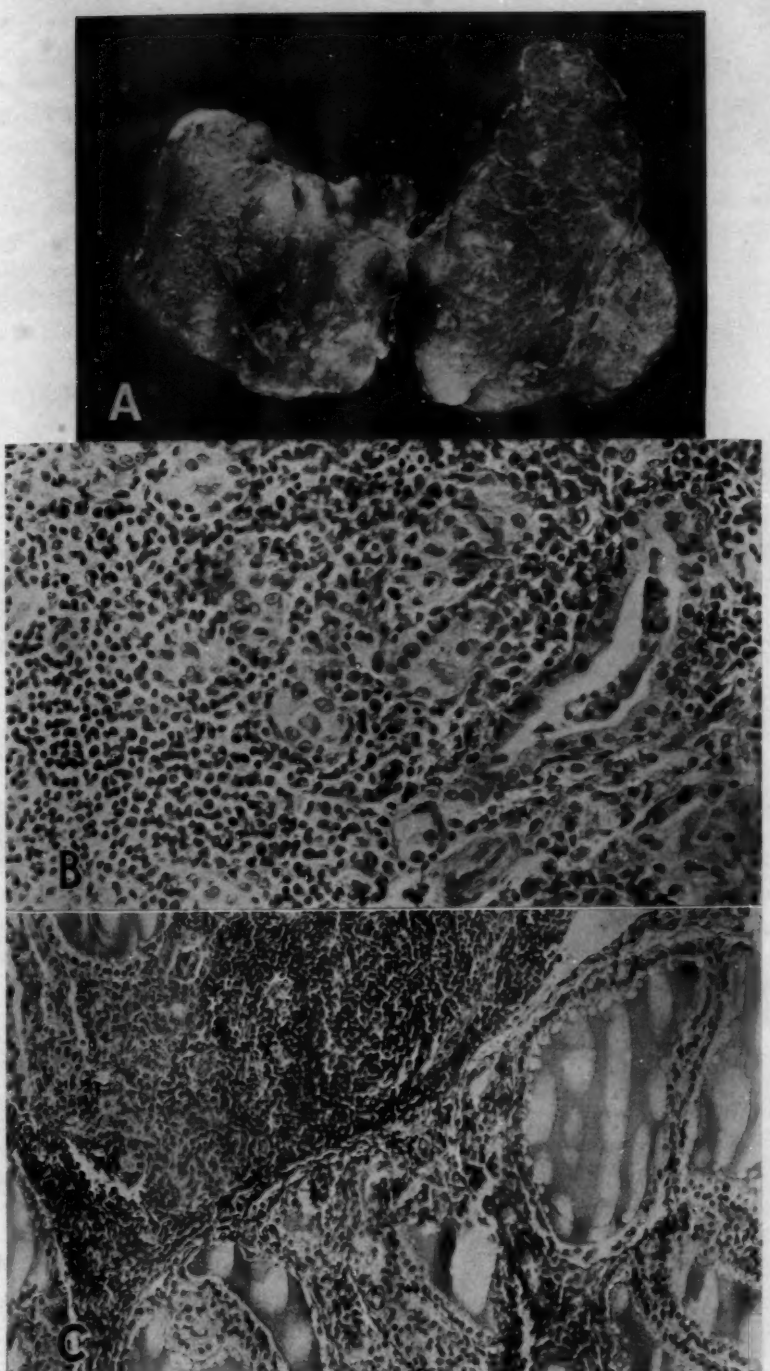

Fig. 3.—*A* is an exophthalmic goiter from a 27 year old woman; *B* and *C* are photomicrographs at different magnifications. The small dry islands seen in the gross specimen are composed of the same colloid-free acini, eosinophilic epithelial cells and lymphoid tissue found in lymphadenoid goiter.

Uhlenhuth,[21] working with thyroid material from salamanders, could show that the activity of the normal thyroid is cyclic. The normal cycle consists of two phases: the colloid storage phase and the releasing phase. During the former, the acinar cells actively manufacture colloid, secreting it in the lumen of the follicle, where it is stored, eventually distending the acinus. During the release phase, the colloid is allowed to escape from the follicles into the blood stream. If the release takes place at a faster rate than the manufacture of colloid, the follicles collapse and assume a starlike shape, the lumens changing into mere slits. According to Uhlenhuth, the release phase is characterized morphologically by depletion of colloid and increase in the height of the epithelium. Normal thyroid function can be maintained only when the release phase is balanced by sufficient secretion and storage of colloid.

Histologic study and clinical experience suggest that in lymphadenoid goiter the normal cycle of thyroid activity is disturbed. The release is much more intense than the manufacture and storage of colloid. In this way the supply of colloid becomes exhausted. On histologic grounds, the same explanation must be accepted for the small dense areas which are found in one fourth of exophthalmic goiters. The acinar cells in these foci have lost the ability to synthesize intrafollicular colloid and do not respond even to large doses of iodine, as given in Plummer's preoperative treatment, by secretion and storage of colloid.

While in exophthalmic goiter the release phase is probably as intensive as in lymphadenoid goiter, one must assume that in general the manufacture of intrafollicular colloid is also increased; otherwise the whole gland would show the same exhaustion as one sees in lymphadenoid goiter. From my studies[22] of European and American goiters, it follows that exophthalmic goiter develops as a rule in diffuse colloid goiter. The latter is characterized by excessive production and storage of colloid. In exophthalmic goiter the acinar cells have retained their ability to manufacture colloid in increased amounts. A short medication with iodine makes this capacity evident, the exophthalmic goiter being converted into a colloid goiter with large, colloid-filled follicles. Only those areas where the cells have been permanently damaged by excessive stimulation stand out as dense islands with colloid-free, small acini, which cannot be differentiated from lymphadenoid goiter (fig. 3 *C*).

As to the causes of lymphadenoid goiter, it is known that there is one agent which produces the same histologic features found in this

21. Uhlenhuth, E.: Tr. Am. A. Study Goiter, 1936, p. 25.

22. Hellwig, C. A.: Surg., Gynec. & Obst. **64**:604, 1937.

type of goiter. In 1926, Uhlenhuth [23] first demonstrated in salamanders that the colloid release phase is affected by the thyrotropic hormone of the hypophysis. Three years later, Loeb and Basset [24] confirmed this observation in mammals.

It has been shown, furthermore, by Uhlenhuth that an injection of the thyrotropic factor will increase the basal metabolism markedly but that with repeated injections this effect soon disappears. Collip [25] has explained this fact by assuming the gradual development of an antithyrotropic substance in animals treated repeatedly with anterior pituitary extract. Such an assumption does not seem necessary, as the drop in thyroid activity coincides with the time at which all the stored colloid has been released. The thyrotropic factor, if given over long periods, impairs the thyroid function, because it interrupts the normal cycle; the colloid storage phase, which is indispensable for normal thyroid activity as well as for prolonged hyperfunction, is frustrated by an excess of thyrotropic factor.

The remarkable results of Uhlenhuth's investigations give the key for the understanding of the causes, histogenesis and function of lymphadenoid goiter. The histologic and clinical peculiarities can be explained best by overstimulation of the thyroid gland by thyrotropic hormone.

SUMMARY AND CONCLUSIONS

The clinical and pathologic features of 4 cases of lymphadenoid goiter are presented. The youngest patient was 16 years old. One patient was followed over a period of nine years. Two surgical specimens obtained from this patient, nine years apart, were identical in structure.

Lymphadenoid goiter is a distinct clinical and pathologic entity.

It is not an inflammatory process but the result of a functional disorder. The cycle of colloid storage and release is fundamentally disturbed, and the exhaustion of colloid explains the symptoms of hypothyroidism, associated so often with this type of goiter.

The underlying cause of lymphadenoid goiter is probably an excess of thyrotropic hormone.

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23. Uhlenhuth, E.: Anat. Rec. **27**:222, 1924.
24. Loeb, L., and Basset, R. B.: Proc. Soc. Exper. Biol. & Med. **27**:490, 1930.
25. Collip, J. B.: Ann. Int. Med. **9**:150, 1935.

Case Reports

CHOROID PAPILLOMA

REPORT OF A CASE

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The benign type of ependymoma originating from the choroid plexus of the fourth ventricle is not uncommon. However, it assumes great clinical importance because of the paucity of clinical symptoms associated with tumors of the posterior fossa in general.

REPORT OF CASE

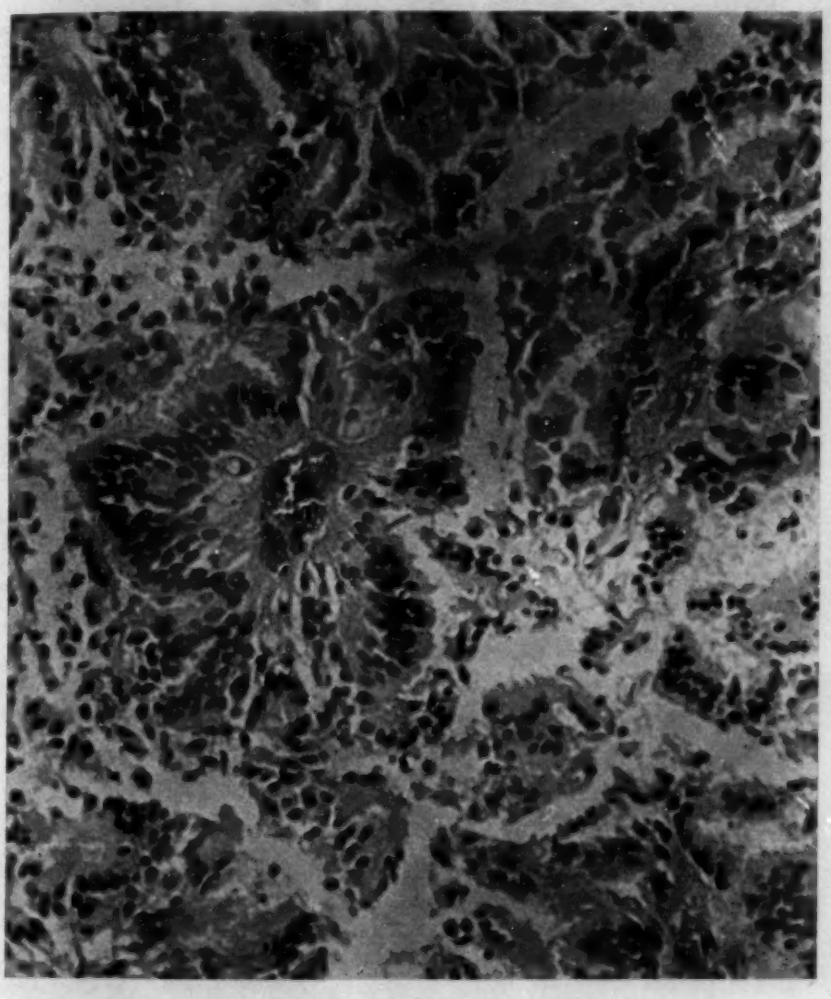
A white man 48 years of age was admitted to the Metropolitan Hospital Dec. 9, 1936. His chief complaint on admission was generalized weakness, especially of all his extremities, pain in the scapular regions and inability to walk. About eleven months before admission he noted that he felt weak on arising in the morning and had a numb feeling in his left hand, which gradually spread to his right hand, left foot and right foot. He also noted that both lower extremities, besides being weak, were moderately stiff. For five months previous to hospitalization he had been bedridden. In addition to the complaint described, he had had some vague gastrointestinal upsets. He was married and had two children, both living and well.

Physical examination on admission gave essentially negative results. The blood pressure was 110 systolic and 70 diastolic. Shortly after admission the following symptoms were noted: slight ataxia on the left, nystagmoid jerks to the left, absence of the abdominal reflexes. The question of cerebellar involvement was considered at this time, but the meagerness of the findings did not permit an immediate diagnosis. Examination of the spinal fluid at this time revealed nothing. Throughout the patient's stay at the hospital little was added to the foregoing findings except the appearance of some questionable dysmetria, so that a possible diagnosis of early multiple sclerosis was considered most likely, especially in view of the fact that, were this a tumor of the posterior fossa, no therapy would be possible.

Repeated examinations of the fundus failed to reveal any papilledema. Vestibular tests showed nothing worthy of note. The Ayala index was 5. The Queckenstedt tests were repeatedly negative. The Wassermann and Kahn reactions were negative. The Wassermann reaction of the spinal fluid was negative. Roentgen examination of the skull showed nothing. July 9, 1937, the patient's temperature suddenly mounted to 103 F., the pulse rate to 118 and the respiratory rate

to 34, and the patient became cyanotic. The chest was full of rales, with dulness and impairment of breathing at the base of the left lung. The following day the temperature rose rapidly to 108 F. The patient died July 10.

Necropsy.—Only a brief summary of the observations will be given. The body was that of a white man 48 years old, who was well developed and fairly well



Papillary structure of the tumor.

nourished. Rigor mortis was present throughout. Livor mortis was present posteriorly. The pupils were equal, regular in outline and in middilatation. Numerous intra-abdominal adhesions were noted, particularly around the porta hepatis. The heart was essentially normal. The lower lobes of the lungs revealed some patchy areas of consolidation. The liver had a parboiled appearance. In the gallbladder the mucosa was streaked with lipoid material—the so-called

"strawberry" gallbladder. The spleen, pancreas, gastrointestinal tract, kidneys, bladder and prostate gland were essentially normal. When the clavarium was removed, the skull was seen to be in normal thickness. The dura and leptomeninges were markedly congested. The cerebral convolutions were flattened. When the infundibular stalk was cut, there was a sudden rush of clear cerebrospinal fluid, which apparently had been under great pressure. On section of the cerebral hemispheres it was noted that the right lateral ventricle contained more fluid and was somewhat more dilated than the left. The brain substance appeared congested. On study of the brain stem it was noted that the fourth ventricle was completely closed off and that the lobes of the cerebellum were compressed by a tumor mass, measuring about 3 cm. in diameter and occupying the medulla from its superior to its inferior portion and from the cephalic to the caudal extremity. The tumor was fairly firm and cut with a moderate degree of difficulty. It had a granular, clustered appearance. The growth deformed the entire superior and inferior aspects of the medulla oblongata and seemingly caused greater pressure and indentation of the left cerebellar hemipshere. It showed no areas of calcification. The brain revealed no other evidence of gross abnormality except for the previously mentioned dilatation of the ventricular system and the congestion of the arachnoid.

Death was due to medullary choke following the increase of intracranial pressure accompanying the development of the neoplasm. There was associated hypostatic pneumonia.

Microscopic Examination.—The tumor had a papillary appearance. The cores of the papillae were made up of fibrous connective tissue and thin-walled vessels of different sizes. The villi were covered with epithelial cells without cilia and containing no blepharoplasts. Special stains revealed a large amount of pigment in these cells. The cells were elongated and possessed faintly eosinophilic cytoplasm with 1 or 2 nuclei and 1 or 2 nucleoli. Some of the nucleoli showed evidence of initial amitotic division. The nuclei contained many granules. In some nuclei no nucleoli were visible. No giant cells were present. No mitotic figures were seen, but the cells showed moderate anisocytosis. Between the villi were some areas of necrosis and some necrotic or fibrinoid material. With special stains we were unable to demonstrate any mucin in the cytoplasm of the cells composing the tumor; neither were any droplets seen which would indicate a secreting epithelium. The tumor was classified as benign choroid papilloma.

COMMENT

According to the study of Agduhr,[1] the choroid plexus of the fourth ventricle comprises two highly vascular fringelike processes continuous with the tela choroidea. We believe that this tumor originated from the invagination of the lower part of the roof of the ventricle, which is made up of a vertical and a horizontal portion. It is known that in the choroid plexus there are many ectodermal elements, and we can consider a tumor of this type to be absolutely of ectodermal origin, in spite

1. Agduhr, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis, Philadelphia, J. B. Lippincott Company, 1926. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

of the fact that the cells show no evidence of a secretory function. The similarity of papillomas of this type to the papillomas of the gallbladder and urinary bladder must be considered as indicating a physiologic activity of neoplastic cells growing in a fluid medium. In discussing the so-called dendritic carcinoma of the breast, the French school [2] emphasized the fact that this type of carcinoma has an inclination to grow close to a blood vessel and that when there is a blood lacuna it grows luxuriously. They call this tumor hemophilic, but we believe that in any neoplasm the cells of the tumor which cannot be nourished on a normal circulation grow more luxuriously when they are in a fluid medium. Therefore, we do not think that it is a question of hemophilism but rather of a physiologic necessity.

In spite of the fact noted in the splendid study of ependymoma by Kernohan and Fletcher-Kernohan,[3] we believe that when the tumor is of the benign papillomatous type the overgrowth is only epithelial and the tumor can be classified as originating strictly from the choroid plexus, but that when the tumor is malignant, as in the cases of Turner and Simon,[4] there is a mixture of choroidal and ependymal elements and the tumor can be classified better as a mixed type and called a choroidoependymal tumor rather than a pure malignant papilloma of the choroid plexus.

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2. Delbet, P., and Herrenschmidt, A.: Atlas du cancer, Paris, Félix Alcan, 1926.

3. Kernohan, J. W., and Fletcher-Kernohan, E. M.: Research Nerv. & Ment. Dis., Proc. (1935) **16**:182, 1937.

4. Turner, O. A., and Simon, M. A.: Am. J. Cancer **30**:289, 1937.

Laboratory Methods and Technical Notes

A MODIFICATION OF TERRY'S METHOD OF RAPID SECTIONING FOR SOFT TISSUES

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Terry's [1] supravital technic has been an important addition to the methods of rapid section diagnosis. Hellwig's [2] modification has proved a time-saving and inexpensive procedure, supplementing frozen section technic. It has found application as a routine diagnostic method for prompt preliminary diagnosis.

Hellwig's modification consists in fixing tissue to a plate of cork by two pins, then sectioning a moderately thin slice, usually 1 mm. in thickness, from the face of this tissue by a common sharp or safety razor blade. This thin slice of tissue is transferred to an ordinary glass slide, superficially stained with polychrome methylene blue for from one to three seconds and washed carefully with tap water to remove any excess of stain. The tissue is then covered with an ordinary cover glass and examined by transmitted light, using a 60 watt Mazda bulb. Stronger or arc light is necessary for transillumination of thicker, dark or bloody tissue. After examination the razor-cut section is preserved in solution of formaldehyde U. S. P. for embedding in paraffin.

In using this method, difficulty was consistently encountered with soft, friable or small fragments. Curettings proved most troublesome. As a result, a modification has been developed which has proved superior to other rapid methods, including that of frozen sections. Whole clumps of fine curetted tissues are examined as readily as if paraffin sections had been made. The procedure is as follows:

A glass cover slip is cemented to each end of an ordinary glass slide, leaving an intervening depressed space from 2 to 2.5 cm. in width and 1 mm. in depth. On this depressed portion is placed the tissue to be examined, including fine fragments. If a large mass is to be examined, this is cut down to a thickness of about 0.5 cm. by scissors, knife or safety razor blade. Curettings are patted together to lie as a flattened but compact mass against the cover slip border. A slight amount of tap water (a drop or two) is added to produce a completely moistened tissue. The slide is then turned over. If the tissues have not been too much moistened, they remain adherent to the glass slide as before. If the fragment or fragments persist in falling off, they may be held in place by the counter-pressure of a 3 inch (7.6 cm.) section of a tongue depressor stick, the ends of the stick and the glass slide being gently maintained between the thumb and second finger of the one hand. The surface of the slide now uppermost is sprayed with ethyl chloride until the tissue underneath is frozen to a depth of from 2 to 4 mm. Again reversing the slide, the tissue is shaved off by firm but delicate application of a sharp common razor blade or preferably a new safety razor blade. Deep or forceful sectioning will result in fragmentation or elevation of the frozen tissue

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1. Terry, B. T.: Am. J. Clin. Path. (Tech. Supp.) **1**:69, 1937.
2. Hellwig, C. A.: Surg., Gynec. & Obst. **61**:494, 1935.

mass. Freezing is readily repeated if there are signs of softening. The tissue, shaved to a thickness of from 1 to 2 mm., is allowed to thaw out, after which polychrome methylene blue is applied for fifteen seconds. The excess of stain is then allowed to drain off, supplemented at times with an extra drop of tap water. The specimen is now covered with a cover slip and examined by transmitted light, a 60 watt Mazda bulb or stronger illumination being used as indicated.

For small fragments this method is superior to ordinary frozen section methods and has proved satisfactory with small and very soft tissues which could not be readily examined by the ordinary Terry-Hellwig technic. It allows excellent differentiation of tissues with polychrome methylene blue. This stain is sprayed on the tissue superficially from an atomizer according to the last article by Terry, in which he described the use of a relatively simple sectioning apparatus to obtain sections of tissue of uniform thickness. In contrast to the staining time used by Terry and Hellwig, it has been found better to leave the stain on the surface of the tissue, spilling over onto the slide, for at least fifteen seconds but not for more than thirty. It is then allowed to drain gently off the slightly tipped slide without washing, which all too frequently destroys color differentiation of tissues and intensity of stain. Likewise, the light used should be of considerable strength, increasing with the thickness of the tissue, its darkness and the amount of blood contained in it. Light of the intensity of sunlight has been found satisfactory. However, when the border of the tissue is the point of interest, with or without the freezing modification, it has been found that the lateral refraction glare from the transillumination may be obviated by a slight excess of stain gathered about the sides of the fragments under the cover slip. For this, the excess drop staining method is still followed. A little practice is required to determine the usual amount of water needed for satisfactory fixation of tissue to the glass slide, so as to allow satisfactory freezing without loss or separation of tissue fragments, unless the counterpressure of a section of a tongue depressor is used. A simple metal clip may be readily prepared by which the glass slide may be held in position on the ordinary carbon dioxide freezing block and the tissue frozen without inversion of the slide. All fragments, together with the preliminary shavings, are subsequently placed in a 10 per cent concentration of solution of formaldehyde U. S. P. to be subsequently embedded in paraffin and sectioned.

Terry's rapid method and the present modification allow good study of tissue structure and, in addition, third dimension views. Fine details of cells, including definition of the nucleolus, so stressed by MacCarty,[3] are clearly presented, remaining thus for from six to eight minutes. It must again be emphasized, however, that interpretation should be made only by those well acquainted with the characteristics of supravitally stained fresh tissue. The details and the size, form, relationships and orientation of cells and the structure of the entire tissue are quite different from what one usually finds in paraffin or frozen sections. Many details difficult to bring out by other methods may stand out prominently; others seem to be suppressed, while the staining values for various tissues and cells frequently are disturbingly altered. Altogether, one finds in various tissues and pathologic conditions a picture open to new interpretation and one which from the esthetic standpoint is often beautiful.

2026 Clay Street.

3. MacCarty, W. C.: J. A. M. A. **107**:844, 1936.

General Review

"ANILINE TUMORS" OF THE BLADDER

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The study of occupational neoplasms has gained increasing scientific and practical importance during the last decade for the following reasons:

1. Experiences obtained from the investigation of these diseases, which are equivalent to experimental cancer in man, have served as a starting point for some of the most momentous discoveries made recently in the field of cancer research, such as the synthesis of numerous carcinogenic hydrocarbons and the demonstration of their chemical relationship to the gonadotropic hormones and to the constituents of bile.

2. Whereas the absolute number of the cases of tumor known to be occupational is relatively small in comparison with the total number of cases of cancer observed, there can be no doubt that the recorded cases of industrial cancer are only a fraction of the number occurring. Supporting this contention are the several new occupational neoplasms which have been brought to attention during recent years, such as osteogenic sarcoma in workers handling radioactive substances (United States), pulmonary tumors in workers handling chromate (Germany) and in workers employed in generator plants (Japan) and pulmonary and nasal cancers in workers employed in nickel factories (England).

3. While the various technical and medical efforts made in the past to prevent the further occurrence of these tumors have been partially successful in decreasing more or less their incidence among workers of certain occupations, none of the occupational neoplasms has been entirely eliminated, in spite of the fact that in several instances knowledge of the causative hazards dates back for a period exceeding one hundred years. The incidence of some of the occupational tumors has become even more widespread owing to the development of certain industries in countries in which such industries had been absent until rather recent times.

To this group of industrial neoplasms belong aniline tumors of the urinary bladder. Not only for this reason are they of special interest. These particular industrial neoplasms have been observed in aston-

ishingly large numbers in the United States during the last six years. In contrast to the majority of occupational neoplasms, the "aniline tumors" develop remote from the sites of primary contact with the suspected carcinogenic agent.

GEOGRAPHIC DISTRIBUTION AND INCIDENCE

The occurrence of occupational tumors of the bladder with a chemical etiology is almost entirely restricted to workers engaged in the manufacture of certain aromatic amines (the coal tar dye industry). Only occasionally have they been reported in workers handling finished dyes (dye mixers, dye grinders, dyers, attendants of dye storage houses) (Schueller; Rosenbaum and Gottlieb; Gay; Leuenberger; Joseph; Fierz-David). Hence these neoplasms have been observed exclusively in countries that have possessed for some time large chemical manufacturing establishments, and in these particular countries they have made their appearance subsequent to the development of such industries. The first cases of this type of industrial tumor were recorded in 1895 by Rehn, in Germany. This country, where the manufacture of coal tar dyes started about 1860, supplied before 1914 more than 80 per cent of the world's production of aniline, aniline derivatives and related aromatic amines. Since that time more than 300 cases of aniline tumor of the bladder have been observed in Germany (Baader; Rehn; Leichtenstern; Nassauer; Oppenheimer; Lewin; Bardenheuer; Bachfeld; Curschmann; Schwerin; Engel; T. Bauer; Brezina; Sebening; Seyberth; Sieben; Simon; Strauss; Ullmann; Teutschlaender; Büttner; Posner). The chemical plants located around Basel, Switzerland, which were established at about the same time as the German chemical factories, were before the World War the only other source of these neoplasms. The first information on cases in Switzerland was communicated by Schedler in 1905. The total number of cases to the present time is over 80 (Leuenberger; Mueller; Henschen). When during and after the great war chemical factories were founded and developed to large scale production also in other parts of the world, aniline tumors soon made their appearance in other countries.

In 1926 Young and Russell noted that there was an excess of bladder tumors among workers of chemical factories and textile dyeing establishments in England. In 1928 Bridge and Henry stated that since 1924 there had been 12 fatal cases of cancer of the bladder among chemical workers. By 1932 the number had risen to 23 and at the present time is in the neighborhood of 40 (in dead and living patients) (Young and Russell; Henry, Kennaway and Kennaway; Bridge and Henry; Bridge; Wignall; Macalpine; Berenblum; Henry; Stallybrass; Report of the Chief Inspector of Factories and Workshops for the

Year 1929). Similar observations were made in the Union of Soviet Socialist Republics by Rosenbaum and Gottlieb in 1926 (3 cases) and by Abramyan, Romberg and Maynats in 1932, and in Austria by Scheele in 1926 and 1927 and by Schueller in 1932. The first cases of aniline tumor in the United States were reported in 1934, i. e., sixteen years after the beginning of the production of synthetic dyes from aniline and aniline derivatives on a large scale. At that time Ferguson and his co-workers placed on record 25 cases, all originating in one chemical concern. The first of these cases was discovered in 1931 by Anderson. The number increased to 86 by the end of 1936, according to subsequent communications (Gehrmann; Wolfe; Evans; Washburn; Gay; Ferguson), and is at the present time approximately 100. The most recent newcomer in this group of countries is Italy, where according to reports of di Maio in 1936 and 1937 12 aniline tumors had developed among 86 workers of a certain dye factory in the course of the last few years. An earlier Italian communication on this subject by Bianchi, in 1911, does not refer to Italian cases but describes some observed in Germany (Carozzi).

The total number of these occupational tumors so far put on record in the various countries is approximately 550. It needs scarcely to be mentioned that this does not represent the total incidence, as numerous factors are at work to obviate accurate information in this respect. It may be pointed out, for instance, that so far all such tumors observed occurred in male workers, in spite of the fact that during the late war women also were employed in these hazardous operations in some of the German plants. While they were eliminated from these occupations soon after the end of the war, it is not likely that all of them escaped without subsequent formation of bladder tumors. It is more probable that when these tumors occurred their occupational origin was not recognized.

Also conducive to reduction in the number of aniline tumors correctly diagnosed is the usual unavoidable turnover of labor in chemical plants. Neoplasms of this type may develop many years after the workman has left the hazardous occupation. He may therefore forget about this occupation or may not mention it to his physician, as he does not realize the existence of a causative relation between some work engaged in many years previously and his present ailment.

It is also possible that not all cases which were recognized or suspected of having an occupational origin have been reported in scientific journals or governmental records. All the American cases, for instance, were observed in the plants of a single chemical company. It stands to reason that similar conditions may exist in other chemical manufactur-

ing concerns producing or handling the same or similar chemicals of the aromatic series. In a discussion of this aspect many years ago Oppenheimer (1920 [b]) complained that factories had a tendency to have their workers treated by factory physicians and in their own hospitals. He added that the statements of the workers among whom such tumors had occurred differed widely from those made by the factory physicians. While the information obtained from the workers is without any doubt unreliable as far as the actual figures are concerned, it cannot be entirely disregarded, since it is to a certain extent supported by the observations of Nassauer. This author found 28 cases of tumor of the bladder among a crew of 105 workers with a yearly transient index of 15 per cent during the years 1892 to 1904. His statements received confirmation from the report of Leuenberger, who noted that such tumors were 33 times as frequent among dye workers as among the rest of the male population of Basel. Similar data were recently published by Mueller (1933 [b]) from Basel.

The frequency of aniline tumors (morbidity statistics) in the working population of different factories evidently varies to a certain extent, depending on the types of chemicals used and produced and especially on the manufacturing processes employed and precautionary measures taken. In addition to these factors influencing the incidence of bladder tumors in different plants, countries and periods, the methods by which statistical data on this subject are obtained are of outstanding importance.

Curschmann pointed out in 1920 that the percentage of aniline tumors among the German chemical workers was actually very low. He found only 177 cases among an estimated 80,000 to 100,000 chemical workers. Also Scheele, in 1926, attempted to discredit any occupational significance in the causation of bladder tumors in aniline workers by referring to the percentages of such tumors in the surgical patient population of the university clinics of Rostock (1.24), Frankfurt (1.81), Vienna (3.59) and Basel (1.66). He pointed out that these figures did not show any relation to the industrial chemical activities in these cities. He argued, therefore, that in Frankfurt bladder tumors were incorrectly attributed to occupational chemical hazards simply because an appreciable part of the population of that city was employed in the chemical industry. In support of this contention he quoted the marked variations existing between the proportions of the different occupational groups contributing to the total number of cases of bladder tumor in the various localities (Fuchs, 25 per cent in intellectual workers; Stenius, 38 per cent among agricultural laborers).

The fallacy in this statistical argumentation is readily evident. It is unessential how high the percentages of the various occupational

groups are in regard to the total number of diseased persons. The significant figure is the number of diseased persons in a certain occupational group. Rehn in 1904 estimated that bladder tumors had been observed in between 0.2 and 0.4 per cent of the workers employed at the different factories where these conditions occurred. Gehrmann stated that in 532 cystoscopically examined dye workers engaged in more or less hazardous operations 25 cases of aniline tumor were detected, i. e., 4.5 per cent. Di Maio (1936), on the other hand, found 11 cases among 54 workers (20.3 per cent). Such figures, however, are not suited to give any reliable information as to the incidence of such tumors in that small group of workers who are engaged in operations in which they receive a more or less continuous and relatively massive exposure (Engel, 1937). The frequency of bladder neoplasms among the members of these small groups of operators runs much higher (from 80 to 90 per cent), especially when technical and sanitary measures are inadequate. As the numbers of workers in these particular groups even in large chemical factories are relatively low, the exceptionally high incidence of bladder tumors among them is not reflected in the frequency rate of these neoplasms calculated for the general population of a larger territory in which the plants are located (Mueller [1936] for Basel; Scheele for Vienna).

There is indication that in more recent years figures of incidence lower than those just quoted have been published for factories which had been conducted over a longer number of years with special technical and sanitary precautions (introduction of a closed production system that eliminates contact with vapors, fumes and dust; extensive exhaust ventilation; careful supervision of repair work; good medical care) (Nassauer; Simon, 1930 [d]). Simon mentioned that in the report of the German Dye Trust only 21 cases of injuries from nitro substances and amino substances were recorded, adding that he had not seen any new cases of aniline tumor in the last four years. Gehrmann noted that according to information which he had received from a German plant operating on a closed production system no new cases had been observed there in the last fourteen years among workers newly employed in that time, a remarkable result in view of the period of latency of these tumors. While it is likely that isolated cases will continue to occur even under the best technical conditions, the frequent, even epidemic-like appearance of cases among the workers of some plants during recent years seems to suggest that the methods of production and the precautionary methods practiced in these factories have not conformed with the requirements recognized as necessary from the technical, chemical and medical standpoints.

ETIOLOGIC AGENTS

The question concerning the chemical character of the carcinogenic agents causing these vesical neoplasms is still controversial in spite of the fact that tumors of this type have been known for more than forty years. While Rehn attributed the development of such tumors first only to fuchsin, which is made by melting aniline, toluidine, nitrobenzene and iron chloride, subsequent investigators have added a large number of substances to the list of suspected carcinogenic agents. The great difficulties which confront the investigator in this respect were pointed out by Hamilton: 1. Workmen handle usually more than one compound and are often shifted from one department to another. 2. Different degrees of danger exist with the same compound when different processes are used. 3. Certain impurities or by-products which occur in traces and are often unsuspected may be more harmful than the parent substance. 4. The nature of the dyes and the methods of producing them vary in different factories.

It was, however, soon recognized that the appearance of bladder tumors was often associated with prolonged occupational contact with the following aromatic bases: phenylamine (aniline), its isomers and homologues (toluidine and xylidine) and other amino derivatives; diphenylamine (benzidine), its isomers and derivatives (e. q., toluidine or dianisidine); naphthylamines and related compounds (e. q., naphthylene diamines).

In addition to these basic substances, some of the various and very numerous other intermediary products (secondary and tertiary arylated and alkylated aromatic amines, such as dimethylaniline) formed during the production of dyestuffs have repeatedly been claimed to be carcinogenic (Engel, 1937). In this connection attention may be called to the many impurities occurring in the commercial aromatic amines, such as betabetadinaphthylamine,alphabetanaphthazine,1,5-hydroxynaphthalene and various other related substances (benzcarbazoles) (Hueper, Briggs and Wolfe; Boyland and Brues; Cook and associates). All aromatic amines with the exception of the sulfonates, aminoanthraquinones and the more complex derivatives irritate the bladder and are therefore suspected of possessing carcinogenic qualities (Engel, 1937). Not only the basic and intermediary substances used in the production of dyestuffs but also the finished products, the dyes, have been mentioned by several authors as causative factors (Curschmann; Schwerin; Oppenheimer, 1920 [b] and 1927, and others). A definite decision in this matter is at the present time not possible, as some of the dyes incriminated often contain aromatic amines as impurities, especially basic dyes of the azin series (e. q., nigrosine, indulin or safranin), or

aromatic amines are used as dye mordants or oxidizers in the dyeing process (e. q., aniline black). It must be pointed out that there is no record in the literature of extensive, systematic and reliable investigations on the potential carcinogenic properties of synthetic dyes, especially of those which may be decomposed in the body into their aromatic amine constituents (Hueper, 1934 [c]; Shear) and thus produce chronic metatoxic effects. A thorough study of this question appears to be highly desirable, as dyes of this type, such as yellow OB (orthotolueneazobetanaphthylamine) have been for some time extensively used for the artificial coloring of foodstuffs (Traub, Gordon and Van Dyke).

A satisfactory agreement also does not exist in regard to the carcinogenicity of the three aromatic amines mainly incriminated (aniline, benzidine and naphthylamine). There is a general consensus that betanaphthylamine, at least in its commercial form, is definitely cancer producing. But there is still doubt as to alphanaphthylamine. While German investigators are doubtful as to this substance and have listed only a few cases in which it was suspected as the activating agent (Engel, 1937), the American authors have attributed, with certain reservations, an appreciable number (about 25 per cent) of the total number) to this substance (Gehrmann; Evans). It is, however, uncertain, whether alphanaphthylamine possesses cancer-producing qualities to any appreciable degree, as the commercial product of German, American and English manufacture contains from 5 to 10 per cent betanaphthylamine as an impurity (Engel, 1937; Gehrmann). The latter substance may therefore account for the carcinogenic response displayed after contact with commercial alphanaphthylamine.

The potential carcinogenic role of aniline appears to be equally uncertain if the statements of German and American investigators are compared. While the German sources are definite as to the carcinogenic qualities of this compound (Engel, 1937) and list 78 cases as caused by it and its homologues, the American authors (Gehrmann; Evans) are equally emphatic that according to their observations the American product does not produce tumors. Evans stated that there was not a single case of tumor of the bladder in a group of 65 men who had been engaged for as long as twenty years in the production of aniline exclusively. The average time of employment of these men was twelve years. They suffered, moreover, frequent attacks of acute aniline poisoning (Wolfe).

It is also doubtful whether pure benzidine base is carcinogenic. According to German sources, none of the workers of a plant in which men came in intimate cutaneous contact with great quantities of powdered benzidine base for many years showed bladder tumors. On the

other hand, it is well established that workers engaged in the production of this compound frequently contract vesical neoplasms. Engel (1937) listed 25 cases in a series of 190 as of benzidine origin and Evans listed 13 cases of a total of 83 as of this origin.

Engel (1937) stated that, of these three aromatic amines, betanaphthylamine appeared to be the most carcinogenic, as it seemed to produce bladder tumors most rapidly and most frequently. In support of his contention he presented the following tabulation:

	Aniline and Homologues	Benzidine	Beta-naphthylamine	Other Bases
Cases	78	25	67	19

Similar relations are apparent from the tabulation published by Evans:

	Benzidine	Beta-naphthylamine	Alpha-naphthylamine	Miscellaneous Aromatic Amines	Alpha and Beta-naphthylamine
Cases	13	16	20	27	7

The high incidence of bladder tumors following exposure to betanaphthylamine is shown by the absolute number listed. It becomes more striking if consideration is given to the fact that in Germany many more men are employed in operations employing aniline than in operations employing betanaphthylamine and that there are 29 additional cases on record in that country in connection with which betanaphthylamine exposure is highly probable (Engel, 1937).

Nitro compounds of the aromatic series are not carcinogenic (Engel, 1937). The mistaken incrimination of these compounds is attributable to the fact that they are used for the production of the corresponding amino compounds. Also the naphthols are apparently harmless (Oppenheimer, 1927), as only a single case of bladder tumor has so far been observed in a worker in a naphthol factory (Posner, 1904).

The hypothesis of Bayet and Slosse and of Hamilton that inhalation of the hydrogen arsenide generated during the production of aromatic amines or contact with arsenic contained in the dye as an impurity is related to the development of bladder tumors in dye workers has been so thoroughly refuted in recent years by numerous investigators (Berenblum; Posner, 1924; Henry, Kennaway and Kennaway; Ullmann, 1926 and 1933; Sieben; Engel, 1937; Hueper, 1934 [c], and others) that it is mentioned here only for historical reasons. The arsenic hazard was eliminated many years since through the replacement of arsenic by nitrobenzene.

EXPERIMENTAL PRODUCTION OF ANILINE TUMORS

Numerous unsuccessful attempts have been made to reproduce these aniline tumors in animals by exposing the latter over prolonged periods to the various aromatic amines (Grandhomme; Jaffé; Schwerin; Posner and Huldschiner; Fischer; Askanazy; Oppenheimer, 1926 [d] and 1927; Adler; Henkel and others). In these experiments various animals were used (mice, rats, rabbits). The mortality among the animals was high. Postmortem examinations showed inflammatory conditions in the lungs and fatty degeneration of the liver and kidneys. With the exception of the temporary acute and the chronic inflammatory and hyperemic conditions in the mucosa of the bladder, nothing was seen indicating a neoplastic response to the substances used.

More recent experiments of Schär (1930) and of Perlmann and Staehler (1932 and 1933) were somewhat more promising, but the results could not be confirmed by Berenblum and Bonser or by Hueper, Briggs and Wolfe. In Schär's experiments 16 young rabbits inhaled ethylbetanaphthylamine hydrochloride, phenylalphanaphthylamine hydrochloride, alphanaphthylamine and betanaphthylamine, respectively, for periods of between six and twenty months. The concentration of the dust was low, so as to imitate the conditions present in the plants. At the end of the experimental period one animal which had been exposed to alphanaphthylamine showed a lesion in the bladder which was interpreted as a fibrous polyp, and a second rabbit revealed epithelial changes in the vesical mucosa which were considered as carcinomatous. These diagnoses, however, have been seriously doubted on various grounds by several authors (Stewart; Berenblum). Perlmann and Staehler, who also employed rabbits but administered betanaphthylamine and aniline, respectively, by daily subcutaneous injections, obtained, after several months (from six to thirty-four weeks) of treatment, fibroepithelial papillary formations in 7 of the 70 rabbits used. Four of the papillomas were present in a series of 40 rabbits treated with betanaphthylamine, while another was found among 30 animals exposed to aniline. This experiment has been repeated recently by Berenblum and Bonser, as well as by Hueper, Briggs and Wolfe, without positive results. The period of exposure and the dose employed in these duplications were even larger than those in the original experiments of Perlmann and Staehler. On the other hand, Hueper, Wiley and Wolfe produced papillomatosis and carcinomatosis of the bladder in female dogs by daily subcutaneous and oral medication with betanaphthylamine (from 300 to 450 mg. daily in capsules) for from twenty to thirty-two months. The lesions observed in cystoscopic and histologic examinations of the bladders of 12 of the 16 dogs thus treated were identical with those seen by these authors in cystoscopic and histologic exami-

nations of dye workers. The tumors continued to grow and became more numerous in some of the dogs after discontinuation of the treatment, during the last six months of observation, while in one dog the first neoplasms in the bladder were noted several months after cessation of exposure. The termination of contact with the carcinogenic agents was thus followed by progression in the appearance and development of the neoplastic manifestations. While none of the 5 dogs which have been killed so far has shown any metastatic deposits at autopsy, 1 dog presented on histologic examination neoplastic penetration into the subserosa of the vesical wall. The recent statement of Ferguson in regard to previous experimental production of bladder tumors in dogs is incorrect and apparently based on faulty translation and interpretation of cystoscopic observations made by Engel (1924) during acute experiments with naphthylamine poisoning.

Berenblum and Bonser, as well as Hueper (unpublished experiments), did not succeed in producing skin tumors in white mice painted for nine months with an ether extract of urine obtained from dye workers with bladder tumors and from dogs treated with betanaphthylamine. This failure may be ascribed to several possibilities. The amounts of carcinogenic substances in the urine may be too small to be effective even after concentration. The chemical manipulation of the urine necessary for extraction may produce a fundamental change in the chemical and biologic properties of these metabolites. The skin of the mouse may possibly be a less sensitive tissue than the mucosa of the bladder of man or of the dog.

Brief reference may be made in this connection to the recent reports of Otsuka and Nagao, who fed rats a diet of unpolished rice to which they had added 0.2 per cent orthometadimethylazobenzol, and to those of Yoshida, who treated animals of the same species with a diet to which 2-amino-5-azotoluene was added. An appreciable portion of the rats surviving more than a hundred days showed papillary and epitheliomatous neoplasms of the bladder mucosa. The chemicals used are chemically closely related to the carcinogenic aromatic amines suspected in the production of "aniline tumors." Rats are in general not suitable for the study of experimental tumors of the bladder, as they suffer frequently from spontaneous and sometimes very extensive papillomatosis of the bladder caused by infestation with worms (Trichosoma crassicaudans) which lodge in the epithelial lining and elicit solid epithelial papillary formations without any participation by, or simultaneous changes in, the submucosal connective tissue during the early stages (Watanabe, 1934 [a]; Löwenstein, 1910 and 1911; Hueckel). These papillary changes remain benign. It would, however, be of interest to know whether they may be transformed into malignant ones on coming in contact with the urinary metabolites of the compounds used

by the Japanese workers, in analogy with the malignant changes produced by Rous in the Shope rabbit papilloma after local treatment with scarlet red. These considerations must also be applied to the report of Brancati, who found a broad-based papilloma at the posterior vault of the bladder in a rat fed for one year with aniline blue (arylrosaniline dye).

In addition to these attempts to produce bladder neoplasms by systemic exposure of animals to aromatic chemicals, numerous experiments have been made to elicit tumorous responses by placing foreign bodies of widely differing chemical composition directly into the bladders of animals. T. Bauer, making a separate pouch in the bladder of the rabbit and painting the mucosa of the pouch for several months with a mixture of tar, scarlet red, aniline and soot, observed the development of papillomas with epithelial metaplasia but without malignant changes. Maisin and Picard introduced into the bladders of rats by cystostomy small plugs consisting of equal parts of tar, paraffin and scarlet red. In 66 per cent of these animals diffuse papillomatosis was seen after the lapse of one month and a half. The tumors were considered in part "histologically malignant," as they showed infiltrative growth. Leone placed in the bladders of guinea pigs and mice pellets of tar, cement, asphalt and licorice. These implantations were followed by metaplastic and keratinizing epithelial changes, with development of papillary processes and infiltrative epithelial growth into the muscular layer under a formation of epithelial cysts. The processes were interpreted as precancerous. By laparotomy Watanabe (1934 [b]) inserted into the bladders of white rats pellets composed of a mixture of tar, scarlet red and paraffin. In 9 of 55 rats thus treated and surviving, he found marked proliferation of the vesical mucosa, which he considered as probably malignant, since alveolar epithelial nests were seen within the muscularis. A critical analysis of the experimental conditions observed in these investigations throws some serious doubt on the value of the results as contributions to the knowledge of the causative mechanism of bladder tumors. The use of a mixture of substances of undetermined chemical and physical character, the presence of surgical trauma of the bladder and the possibility, if not even the probability, of the preexistence of parasitic papillomatosis of the bladder are complicating factors which interfere greatly with reliable interpretation of the results reported.

CAUSATIVE MECHANISM

The carcinogenic aromatic amines mentioned may enter the organism through three systems: the respiratory, the alimentary and the cutaneous. The majority of investigators agree that the main entrance is

through the lung, because of the inhalation of these substances in the form of fumes or dust (Rehn, 1906; Oppenheimer, 1920 [b]; Nassauer, and others). The gastrointestinal tract is usually discounted as a place of resorption of major significance on account of the general precautionary measures taken by the workers in chemical factories, such as washing the hands before handling food (Leuenberger), and on account of the low solubility of these compounds in water, which impairs their resorption through the intestinal mucosa. But Gehrmann has justly pointed out that whenever such precautions are not taken, owing to ignorance or negligence, gastrointestinal resorption may add to the amount of these substances entering the body through the lungs and skin. A part of inhaled dust is, moreover, swallowed and thus enters the gastrointestinal tract. It seems also to be doubtful whether the low solubility of the aromatic amines in water acts as a preventive to resorption in the intestine, as fatty substances are usually present in sufficient amounts to serve as solvents and thereby to facilitate penetration into and through the mucosa. It can easily be shown that acute as well as chronic poisoning of animals can be readily obtained with oral feeding of the aromatic amines. The absence of these compounds from the feces excreted is additional proof of their effective resorption.

As all aromatic amines are soluble in lipoids they penetrate the skin rapidly, a fact which is satisfactorily demonstrated by the numerous cases of acute aniline poisoning observed among workers following cutaneous contact with aniline and by the accidental occurrence of such poisoning on the wearing of shoes dyed with compounds containing aniline. Cutaneous absorption of appreciable amounts of naphthylamine and benzidine is not likely to occur under ordinary occupational conditions, as these substances are solids.

In the present state of knowledge no definite decision is possible as to whether the aromatic amines as such or their organic oxidated conversion products are responsible for the carcinogenic action. Conversion products have been demonstrated in the urine for aniline, dimethylaniline, benzidine and both naphthylamines (Engel, 1920, 1924 and 1927). They are partly excreted as aminophenols, partly as aminonaphthols. Klingenberg showed that aniline is hydroxylized in the body and excreted with the urine as para-aminophenol ether sulfate (Schmiedeberg), a substance considered by Leuenberger as the main carcinogenic agent. But Engel (1920 and 1924) pointed out that there are several aromatic bases suspected of carcinogenic qualities which do not undergo this change in the body (e. q., paratoluidine) because the para group can be hydroxylized only into an amino group when the para position is not occupied by another group (methyl group in paratoluidine). Adler, however, reported that benzidine and substances

with occupied para position when fed to rabbits and dogs undergo hydroxylization. The controversy was finally settled by Weber and Heidepriem, who could show that the results of Adler were due to the use of unsuitable methods of extraction and therefore incorrect. Rambousek, on the other hand, asserted that the aniline derivatives excreted with the urine in partly or completely detoxicated forms are not the dangerous fractions but that the part which is responsible for the injurious effect is the 1 per cent of the total amount introduced which remains in an unchanged form in the blood, leaving the body with the respiratory air.

Engel (1920 and 1924) concluded from acute experiments in which he gave dogs large amounts of betanaphthylamine that this substance is quantitatively transformed in the body and excreted with the urine as a univalent or bivalent aminonaphthol bound to sulfuric acid or glycuronic acid. This statement, however, is open to doubt, as Engel calculated the amount of aminonaphthol excreted indirectly from the amount of sulfuric and glycuronic acids found in the urine. This must be considered as a rather unreliable procedure in view of the fact that the introduction of manifestly toxic doses of betanaphthylamine causes degenerative changes in various organs (liver, kidney, spleen, lymph nodes, blood, testes [Hueper, Wiley and Wolfe]), which in turn may give rise to an increase in the urinary excretion of the aforementioned acids, unrelated to that caused by detoxification of the aromatic amines. It appears also likely that there are other conversion products contained in the urine in addition to the one mentioned.

Mayer suggested that possibly hypersensitivity is involved in the causation of aniline tumors. In support of this hypothesis he pointed out that some of the related aromatic amines (paraphenylenediamine and other ursol compounds) are responsible for the frequent occurrence of occupational dermatitis, asthma and rhinitis on an allergic basis among fur dyers. The supposition is that some of the conversion products formed in the body from the carcinogenic aromatic amines are chemically highly reactive quinogenic substances which can easily combine with protein complexes and thus form chemospecific antigens. Hueper (1936) and Hueper, Briggs and Wolfe have recently dealt with this aspect of the causative mechanism of aniline tumors in two communications which discuss the chemoimmunologic and histologic evidence which seems to favor such a conception (Landsteiner; Marrack; Klopstock and Selter; Boyland and Warren; Creech and Franks; Reuterwall, and others). Attention may also be called to a paper of T. Bauer on the serum antibodies against various endocrine and other organic substances containing phenol groups, as the antibodies produced showed chemospecific qualities in the presence of the phenol group and

thereby demonstrated the possibility that similar systemic immune reactions may follow the introduction of aromatic amines.

Cook and his co-workers suggested that the carcinogenic metabolite of betanaphthylamine is 3,4,5,6-dibenzcarbazole, as this may easily be formed from betanaphthylamine in the body. Boyland and Brues showed that 3,4,5,6-dibenzcarbazole when painted on mice causes the development of skin tumors. Proof that this substance is formed in the body after the latter's exposure to betanaphthylamine is still lacking.

None of these investigations has provided as yet definite information as to the exact nature of the carcinogenic agent or as to the mechanism of its action on the cells of the bladder mucosa. It has remained doubtful even whether these substances are directly or indirectly carcinogenic, i. e., whether they elicit a neoplastic response in a predisposed tissue or produce a conditioning of the mucosa such that other substances may induce the tumorous response (Latzko). In reference to these considerations Scheele (1926) pointed out that in general substances which produce a cancerous predisposition are also carcinogenic (tar).

There may be mentioned in this connection a proposal made by Stallybrass, who suggested an investigation of the combined action of amino bases and arsenic in the production of bladder tumors on the assumption that the effects of the two substances may be synergistic. Such an experiment appears to be appropriate in view of the fact that prolonged ingestion of small amounts of arsenic on vegetables and fruits is not uncommon in recent years since the introduction of arsenic-containing sprays as insecticides.

Kuchenbecker devised a qualitative test for the demonstration of aromatic bases in the urine of persons exposed to these compounds. By diazotizing these substances in the urine and coupling the resulting products to the sodium salt of a phenyl or benzoyl derivative of 2,5,7-aminonaphthol sulfuric acid a reddish compound is obtained. Kuchenbecker claimed for his test also quantitative effects, but Berenblum commented that the test is good only for qualitative results and is unreliable in quantitative respects. Kuchenbecker found the largest amounts of aromatic amines in the urine of workers exposed to inhalation of the substances in the form of dust.

TIME OF EXPOSURE AND PERIOD OF LATENCY

In conformity with observations made on occupational tumors in general, aniline tumors will ensue as a rule only after a relatively long time of exposure to the carcinogenic agents. Although no definite information exists concerning the minimal time necessary for eliciting a blastomatous change, the statements made on the subject by various authors place the minimal period in general at two years. Koelsch,

however, contended that an exposure of only six months to betanaphthylamine may be sufficient to cause subsequently a neoplasm of the bladder.

Oppenheimer (1927) recorded that in his series the period of exposure ranged from one to forty-one years, with an average of seventeen years, while the first symptoms were observed after from eight to forty-one years of exposure, with an average of eighteen and a half years. Mueller's (1936) observations on the subject are similar (exposure period, from two to twenty-eight years; first clinical symptoms, after from nine to twenty-eight years, with an average of eighteen years). Henschen gave the average length of exposure as seventeen years (range, from two to thirty-five years); the average time of exposure for benign tumors in his experience was fourteen years and four months and that for malignant neoplasms nineteen years. In a series of 105 instances collected by Hueper from the literature several years ago the incidence of tumors after various periods of exposure appears as follows:

Years	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40
Cases	10	13	25	28	14	9	3	3

Evans arranged his 83 cases according to duration of exposure as follows:

Years	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40
Cases	11	20	28	21	2	1	0	0

A comparison of the two tabulations reveals the fact that in the American series of Evans 71 per cent of the tumors appeared within from one to fifteen years after exposure, while in the European series of Hueper only 46 per cent developed within the same time of contact. Whether or not this indicates differences in degree of exposure remains at the present time a problem for research. Attention may, however, be called to the fact that in the majority of the American cases the exposure was to betanaphthylamine, which, according to Engel (1937), is apt to cause a neoplastic response more quickly than the other aromatic amines.

A characteristic feature of aniline tumors which is of great medical, medicolegal and social importance is that they may develop many years after cessation of exposure to the carcinogenic agents. Nassauer reported that in some of his cases tumors appeared from one to seventeen years (average eight years) after the termination of the hazardous work. This phenomenon is not unique, as similar observations have been made in regard to the time of manifestation of carcinoma due to arsenic, tar, soot and to roentgen rays. A reliable explanation of this peculiar behavior is, however, still missing. It may be assumed

that the exposure produces at the time a conditioning of certain cells or cell complexes in the wall of the bladder which may make them especially sensitive to normal or abnormal stimuli of growth. Whenever this cell-fixed quality can exert itself, owing to lack of normal growth-restraining influences or to an excess of agents promoting proliferation, tumor formation will result.

The length of exposure has been related to the biologic characteristics of the ensuing tumors (Henschen). It was assumed that the neoplasms were primarily benign and were transformed subsequently into malignant growths as contact with the carcinogenic substances continued. This was soon recognized to be incorrect, as it was observed that malignant tumors may develop as early as benign ones (Oppenheimer, 1926 [d]; Curschmann). This conception is confirmed by Hueper's (1934 [c]) compilation of 93 instances recorded in the literature:

Years	1-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40
Benign tumors	2	0	2	4	4	2	0	0
Malignant tumors	8	13	16	24	8	5	2	3

Furthermore, histologic observations in sections from the bladders of dogs with aniline tumors furnished definite proof that many of these neoplasms are malignant from the start and do not pass through a benign stage (Hueper, Wiley and Wolfe).

Engel (1937) is, on the other hand, of the opinion that the benign or malignant character of a bladder lesion has a certain relation to the chemical nature of the aromatic amine which caused it. Tumors resulting from exposure to betanaphthylamine are, according to his contention, more likely to be papillomas, while those following contact with aniline, benzidine and their homologues are more frequently primarily malignant. He offered the following compilation in support of his claim:

	Aniline and homologues	Benzidine	Betanaphthylamine	Other Bases
Cases of papillomatosis	11	5	16	5
Cases of carcinomatosis	25	22	15	5

An analysis of the data furnished by Gay in regard to the American cases seems to support to a certain degree the opinion of Engel (1937). Among 59 bladder tumors diagnosed histologically, 29 were malignant and 30 were benign; that is about the same ratio as found by Engel for the betanaphthylamine tumors. In view of the fact that the majority of the American patients had been exposed to betanaphthylamine and considering that most of their lesions were relatively early, some support can be given to Engel from this source.

AGE

It has been asserted that bladder tumors having their genesis in exposure to aromatic amines appear in an earlier period of life than those of unknown cause. Schär stated that aniline tumors are especially frequent in men between 30 and 40 years of age. Büttner found that the average age of the afflicted workmen was 48, the youngest being 38 and the oldest 54. Oppenheimer (1927), on the other hand, noted that malignant tumors are not frequent in men between 30 and 40 years of age. The fifth decade was, according to him, the period during which the majority of aniline tumors were seen. The 94 instances collected from the European literature by Hueper (1934 [c]) were distributed in the various age periods as follows:

Years	20-30	31-40	41-50	51-60	61-70	71-80	81-90
Hueper's series of European cases	1	12	32	42	7		
Evans' series of American cases	5	19	23	29	6	1	
Joseph's series of cases of unknown origin		13	32	46	41	21	4

The two series of aniline tumors both show a definite shift toward the younger age groups in comparison with the series of unknown origin. These observations contradict the statment of Engel (1937) that aniline tumors are rarely seen before the fiftieth year. Engel conceded, however, that they may occur at an earlier age if the workers are exposed to a very active carcinogenic substance, such as betanaphthylamine. The American series, with its high proportion of patients exposed to the compound mentioned, apparently confirms this part of Engel's contention, as it shows a marked shift toward the younger decades of life.

In view of the fact that many of the workers in dye factories entered employment at a rather early age, the foregoing observations present important support for the conception that not the age but the duration of exposure is the determining factor in the development of aniline tumors (Curschmann; International Labour Office; Kennaway).

On the other hand, age, inasmuch as it goes parallel with duration of exposure, may have some relation to the biologic character of the aniline tumors observed. It appears that with increase in age there is a corresponding appreciable increase in the proportion of the malignant neoplasms, as is evident from the following evaluation of 62 instances collected from the European literature:

Years	20-30	31-40	41-50	51-60	61-70
Benign tumors	1	2	3	2	0
Malignant tumors	0	6	22	29	7

As the European tumor of this type is usually not discovered during an early developmental stage, these figures suggest the possibility that some of the benign tumors undergo malignant transformation at some point in their course and thereby increase the proportion of malignant tumors in the older age groups.

CLINICAL SYMPTOMS

As aromatic amines are hemotoxins (methemoglobin formers) acute anilism is characterized by cyanosis, usually associated with stranguria, hematuria and symptoms of transient cystitis (Bachfeld). Rossbach, who in 1885 recommended naphthylamine as an intestinal antiseptic, recorded similar symptoms in patients who were subjected to this medication. Engel (1920 and 1924) observed these manifestations in dogs acutely poisoned with betanaphthylamine. But such attacks are not definitely known to have occurred as a result of exposure to this substance during its production and handling (Engel, 1937). Apparently, acutely toxic doses are thereby rarely introduced (Mueller, 1936). In view of the fact that frequently there have been no acute attacks of cyanosis and urinary symptoms in the lives of persons afflicted with aniline tumors, it is highly doubtful whether such occupational episodes are of diagnostic or causative significance. In only 13.5 per cent of Anderson's 23 cases did the patient give a history of urinary disturbances preceding the discovery of the tumor. Washburn reported that 52 per cent of the patients showed no symptomatic evidence of tumor of the bladder. Wolfe related that only 4 of 65 patients had hematuria, urgency and frequency of urination and that all 4 had well advanced tumors. Only a few of the remaining patients showed occasional red blood cells in the urine. Aniline tumors therefore do not produce during their early developmental stages any subjective symptoms, and these may be absent even when the neoplasms are well advanced. But hematuria, intermittent or constant, is the most frequent early symptom. Other subjective complaints more or less often noted during later stages of the disease are stranguria, burning sensation at urination, pain in the region of the bladder, frequent micturition, oliguria, difficulty in urination and passing of shreds. For a long time the symptoms remain purely local, and the general health is not seriously affected.

These observations show convincingly that the only reliable and effective means of early discovery is offered by periodic cystoscopic examinations of the persons exposed (Oppenheimer, 1926 [d]; Gehrmann; Baader). Unfortunately, such a procedure meets not infrequently with resistance on the part of the workers (Wolfe). It is for this reason that in the German and Swiss plants cystoscopic examinations are not done as a routine but only when hematuria has been demonstrated repeatedly. Urinalyses are then performed at intervals as a routine.

Engel (1937) stated that cystoscopic examination may show three morphologic types of lesions of the bladder in chronic poisoning with aromatic amines:

1. Lesions due to chemical irritation of the bladder. The bladder presents hemorrhagic spots, situated mainly in the trigonal space and around the ureteral and urethral orifices. This reaction usually recedes within from two to three weeks. Months or years later tumors may be rarely observed in the same areas in which the hemorrhages occurred.

Wolfe observed these "submucosal hemorrhages" of varying size and extent in some of his patients, especially during the summer months, and commented that on subsequent cystoscopic examinations the hemorrhages had disappeared, leaving the bladders of these patients clear and normal. Reference to the presence of such hemorrhagic spots in the mucosa of the bladder of the dye worker was first made by Simon (1932), who observed the development of tumors at the sites of these spots several years later. Gay and di Maio (1937 [*c*]) described them as hyperemic spots, resulting from capillary hyperemia and telangiectases (spider vessels). They were usually located in the lower half of the bladder, where the convolutes of dilated vessels caused slight local elevations of the overlying epithelium. While Simon, di Maio and Ferguson asserted that these lesions are precursors of tumors and that thereby the future occurrence and location of bladder neoplasms can be predicted, Engel (1937), Berenblum, and Hueper, Wiley and Wolfe came to the conclusion that they are not of precancerous character but represent transient acute vascular reactions of the vesical mucosa.

2. Benign papillomas. These may be polypous or villous, pedunculated or sessile, and are often multiple. They are most often located in the trigonal and paratrigonal region, especially around the ureteral orifices.

3. Carcinomas. These are usually broad-based papillary tumors, but nodular infiltrative neoplasms also occur. They are situated, according to Engel (1937), with equal frequence in all parts of the bladder, unless they develop from primary papillomas. In the latter case they are most often found near the ureteral orifices and in the anterior and posterior walls, as well as near the urethral orifice. They are rarely located in the renal pelvis or in the posterior part of the urethra.

Similar lesions were seen cystoscopically in the bladders of dogs exposed to subcutaneous and oral administrations of large amounts of commercial betanaphthylamine (Hueper, Wiley and Wolfe). They may be divided according to their appearance and character into three groups:

1. Transient inflammatory and vascular reactions. The most frequent and earliest pathologic manifestations were represented by well defined "hemorrhagic spots." These consisted as a rule of localized con-

volutes of engorged capillaries, to which occasionally highly hyperemic and tortuous larger vessels extended in radiating formation. In other instances the red stipplings were definitely hemorrhagic extravasations. Multiplicity and group formation were a striking characteristic of these lesions. Areas of bullous edema were rarely seen. In a few instances there were also small sloughing mucosal ulcers. The mucosal hemorrhagic spots were frequently of highly transient nature and disappeared without leaving a trace, so that it appears improbable that these vascular manifestations represent precancerous lesions.

2. Localized mucosal thickenings. These were well circumscribed orange to brown-red or blanched areas, with or without elevation, showing occasionally tiny raised points, which on subsequent examinations often definitely had the appearance of early papillomas. The surfaces of these foci were sometimes rough and bled easily. Spontaneous regression of this type of lesion was observed repeatedly, but more often there occurred progressive development into a tissue response that was definitely neoplastic. In contradistinction to this tumors also appeared in areas which had not shown evidence of preceding mucosal abnormality.

3. Tumors. The neoplastic proliferations were usually of a papillomatous type. Many were pedunculated; others were sessile and of broad base. Many of the early lesions had the appearance of small edematous mucosal polyps. The well developed papillomatous growths were in general composed of rather plump villi, sometimes showing hemorrhagic tips or sloughing lesions. Delicate, feathery papillomas were uncommon. Infiltrative nodular tumors were observed in several instances. Neoplastic multiplicity was the rule, often attaining the status of general papillomatosis.

In contrast to the human tumors with their most frequent site on the floor of the bladder, the canine neoplasms were most often found in the region of the dome and the adjacent parts of the anterior and lateral walls. Tumors located on the proximal portion of the posterior wall and on the floor of the viscus were relatively rare and usually coexisted with general papillomatosis.

The incidence of pathologic lesions of the bladder increased, according to the observations of Hueper, Wiley and Wolfe, with the duration of exposure, not only in the entire series of 16 dogs but also in the individual animal. There was at the same time an increasing frequency of definitely neoplastic lesions.

HISTOLOGY

In structure the lesions occurring in the bladders of workers exposed to aromatic amines vary greatly. Some are purely or mainly of inflammatory type; others present epithelial hyperplasia as their most

prominent morphologic feature, being identified thereby as precancerous, while a third group is definitely neoplastic. Whereas a reasonable amount of information has existed for some time concerning the histologic structure of the tumorous formations, little is known in regard to the other two types of lesions mentioned. It is only in recent years, through several observations of Rössle and Teutschlaender and the work of Gay and Ferguson, that histologic data became available concerning some of the moderately early changes occurring in the submucosa and mucosa of the bladder of the dye worker. The two last-mentioned authors rendered the following description of these lesions, from which they drew certain conclusions in regard to the formative mechanism of aniline tumors.

The terminal capillaries in the mucosa become dilated and surrounded by lymphocytes. The vessels resemble miniature varices and are composed of thin-walled spaces, lined with endothelium but lacking in smooth muscle. Somewhere in the vicinity there is usually a vessel showing concentric proliferation of the endothelium. The lumen of such a vessel is consequently narrowed or occluded, and this plausibly explains the dilatation of its afferent capillaries. Increased intracapillary pressure plus continued action of the toxic agent may then result in further endothelial proliferation with the formation of new vascular spaces. The occluding mass of endothelium is gradually replaced with connective tissue, which becomes hyalinized. A natural result of the congestion is exudation. Edema and a few cells from the blood are therefore frequently to be seen in the surrounding tissue. The presence of numerous lymphocytes and occasional eosinophils in the subepithelial tissue suggests chronic irritation. In the early lesions the epithelium and connective tissue are inactive. Ferguson assumed that the next step is fibrosis and the growth of new capillaries beneath the basement membrane of the mucosa, followed by rapid multiplication of the basal epithelial cells of the mucosa. The hyperplasia of these cells plus the activity of the submucosa causes the mucosa to become raised and at a later stage to form papillary projections, subsequent to which the neoplastic basal cells break through the superficial layers with resultant formation of a typical papillary carcinoma. Gay, on the other hand, noted that the vascular lesion may disappear and the area remain normal or there may appear at this site later on an epithelial tumor. The latter event is characterized microscopically by a variety of changes. The cells may become vacuolated. Small cysts are formed, and there may be cystitis cystica. Often the epithelium is locally atrophied. The earliest neoplastic lesion consists of a proliferation of the basement layer of the epithelium in the form of a simple projection of the vesical epithelium with a mass of blood vessels extending into it from its base.

In other instances the proliferation shows a downgrowth, which may extend under the adjacent normal epithelium.

The histologic structure of the aniline tumors is stated to be anatomically identical with that observed in bladder tumors of unknown cause. More detailed information as to the different types and their relative frequency is not readily obtainable from the descriptions in individual case reports. Gay has grouped his 61 cases according to the grade of histologic malignancy as follows:

Early lesion	2
Papilloma, grade 1	30
Papillary carcinoma, grade 2	14
Carcinoma, grade 3	9
Carcinoma, grade 4	1
Carcinoma, ungraded	2
Mixed grades	3

Among them were tumors with squamous and adenoid features, but none was of sarcomatous type.

I have had the opportunity to examine and evaluate biopsy sections obtained from bladder lesions found in 67 dye workers (125 specimens, 25 of which represented early lesions, such as inflammatory reactions, mucous polyps, polyps with papillary epithelium and leukoplakia) and similar sections removed from 14 dogs which had been exposed to commercial betanaphthylamine and had acquired bladder tumors (85 biopsy specimens). I studied, in addition, numerous sections prepared from the bladders of 5 of these dogs which came to autopsy. Four of them showed grossly diffuse papillomatosis. One had remained cystoscopically normal. In view of the fact that neither a detailed nor a systematic presentation of the histologic character of preneoplastic and neoplastic lesions of the bladder caused by aromatic amines has been rendered, the following description is given, based on the evidence mentioned and representing a composite picture of the various changes seen in man and dogs.

Non-Neoplastic Lesions.—The non-neoplastic lesions of the bladder can be divided into the following types:

1. Inflammatory reactions (simple and ulcerative, i. e., irritation bladder and aniline ulcer [Henschen])
2. Intra-epithelial abnormalities
3. Leukoplakia (simple, papillary and infiltrative)
4. Mucous polyps (simple, papillary and infiltrative)

1. Inflammatory reactions of chronic type. These were occasionally observed in man and dogs. Such a lesion appeared cystoscopically as

a small reddish edematous elevation, sometimes surrounding a small mucosal defect or assuming the shape of a short polypous or warty protrusion.

The epithelial lining over the lesion was often atrophic; i. e., it consisted of two or three layers of small pyknotic and vesicular epithelial cells. Epithelial defects were not rare, especially in the polypous manifestations. The defects were either filled with chronic inflammatory granulation tissue or presented a bare connective tissue surface. A thickened epithelium was present in a few instances. The subepithelial connective tissue was always more or less edematous. In several lesions this condition reached such a degree that the epithelial lining was lifted from its supporting tissue and an ill defined serous subepithelial blister formed (bullous edema). The stroma, especially beneath the mucosa and around blood vessels, was usually mildly to moderately infiltrated by lymphocytes, with not infrequently an appreciable admixture of eosinophils. Loose eosinophilic accumulations occasionally filled the subepithelial capillaries. The vascular network in the submucosa was often dilated and denser than normal, while varicose and ectatic capillaries were commonly found in the polypous formations. Knoblike endothelial proliferations were present only rarely and when present were in general associated with, or were contained within, small edematous polypous protrusions.

The endothelial granulomas which were found attached to the walls of precapillary, and occasionally also to ectatic capillary, vessels varied somewhat in appearance, depending on the age of the lesions and their size. In some vessels the endothelial lining showed localized endothelial proliferations, consisting of small clumps of swollen endothelial cells projecting like small polyps into the vascular lumens. With increasing size and age these knoblike protrusions became less cellular and more hyalinized, ultimately causing complete occlusion of the affected vessels. The walls of such vessels were sometimes thickened by concentric layers of endothelial cells. There was in general no perivascular lymphoid accumulation connected with this type of endothelial obliterative angiitis. Perivascular fibrosis and hyalinization were, on the other hand, frequently associated with it.

Large focal lymphoid accumulations, occasionally containing centers of paler stained large cells, were characteristic of the inflammatory condition in some instances. These lymph follicle-like formations, which either were located directly beneath the epithelial lining, sometimes penetrating and replacing it, or formed the centers of larger edematous protrusions, were surrounded by loose connective tissue, often containing eosinophilic cells and old blood pigment. This peculiar type of lymphoid manifestation was the only morphologic response demonstrable in repeated biopsy sections removed from a dog which even

after thirty-two months of treatment with betanaphthylamine did not show any neoplastic lesions. Similar lymphoid tissue reactions were observed in several biopsy specimens obtained from dye workers. Whether this particular type of morphologic reaction in the bladder is indicative of a special type of biologic response cannot be decided from the evidence available.

It can, however, be stated that inflammatory manifestations evidently play no important or essential part as precursors of the development of neoplastic conditions. Their occurrence must be attributed to the presence of cytotoxic substances in the urine which, when resorbed, elicit the inflammatory chemotoxic response.

2. Intra-epithelial abnormalities. Localized pathologic changes in the morphologic character and arrangement of the epithelial cells in the mucosa of the bladder have so far not been observed in man, apparently on account of technical difficulties. They are, however, frequently observed in the bladders of dogs exposed to betanaphthylamine and are considered as the earliest pretumorous response of the mucosa to the carcinogenic agent.

In such lesions the epithelial lining is in many instances thinned, consisting of small pyknotic cells, ill defined, closely packed, irregularly arranged and occasionally forming indistinctly outlined intra-epithelial nodules. In other instances it is composed of cells with vesicular cytoplasm and small hyperchromatic nuclei. The irregularity of the cells in size, shape, arrangement and stainability was sometimes so marked that the lesion had the appearance of a noninfiltrative carcinomatous coating, similar to that observed in the human uterine cervix. There were also areas made up of small, indistinctly contoured, hyperchromatic cells arranged in numerous short pointed or tonguelike solid epithelial papillae. The basal line of the epithelium in all the conditions just described was sharp and straight. There were no vascular or connective tissue changes in the submucosa. In some instances the small intra-epithelial nodules had partially separated from the epithelial lining and seemed to drop off into the submucosa.

3. Leukoplakia. The mucosa consisted of a markedly thickened epithelium, composed in the deeper layers of transitional cells and in the more superficial layers of large polygonal cells. The cells were usually irregular in shape and size and often swollen, vesicular or balloonlike. Small intraepithelial cysts, apparently resulting from localized liquefaction necrosis within the epithelial mucosa and filled with a bluish or pink-staining homogeneous matter, were often found. In some of these lesions the epithelium was arranged in short, indistinctly demarcated plump solid epithelial papillae. Rounded or pointed epithelial pegs,

usually but not always distinctly outlined, and extending into the subepithelial connective tissue, were a characteristic feature. In some instances the loss of polarity was complete. Large, ill defined round or polygonal epithelial cells infiltrated beneath the mucosal lesion in small groups and strands or as individual cells, penetrating the submucosa and producing the picture of a minute anaplastic carcinoma. The epithelial changes described resembled in many respects those seen in the skin as morphologic expressions of precancerous roentgen ray and arsenical dermatosis.

The subepithelial connective tissue was usually edematous and infiltrated with lymphocytes and leukocytes, which were at times predominantly eosinophilic. Brown-pigmented phagocytes occurred in several instances in larger number in the connective tissue directly beneath the epithelial mucosa. The capillaries were often dilated and hyperemic in the more advanced lesions, which showed also an increased density of the capillary bed. Newly formed capillaries extended sometimes from the submucosa through a highly edematous subepithelial zone into an indistinctly outlined and irregularly arranged mucosa. Their content of eosinophilic cells was remarkable. Endothelial granulomas were found in about 50 per cent of these leukoplakic lesions. Some of the most advanced and even early malignant changes of this type were not accompanied by inflammatory or vascular reactions of the submucosa. In those instances the epithelial cells invaded diffusely an apparently normal submucosa.

4. Mucous polyps. The small knoblike mucosal protrusions with narrow pedicles found in the bladders of dye workers and dogs exposed to aromatic amines showed many of the histologic features just described. The epithelial lining of some of these mucosal polyps was composed of an atrophic, thinned pyknotic or vesicular epithelium, occasionally containing small defects filled by chronic inflammatory granulation tissue or presenting a bare connective tissue surface. In other instances the epithelium consisted of from several to many layers of swollen, round-shaped vesicular epithelial cells with pyknotic nuclei. Multinucleated large cells and huge cells with giant-sized hyperchromatic nuclei were sometimes scattered in the hyperplastic mucosa, especially near the tips of the polyps. Markedly thickened portions of the epithelium contained also at times epithelial nodules and pseudoglandular cysts. A number of these polyps showed small solid epithelial or fibroepithelial papillary projections extending from the surface, while others showed epithelial pegs and processes invading the submucosa. The latter processes were in several instances highly infiltrative and markedly atypical in cellular character, suggesting an early stage of anaplastic malignant change. These malignant transformations usually involved the tips of the polyps.

The stroma consisted of an edematous, loose and in general very vascular connective tissue, often infiltrated with lymphocytes and eosinophilic cells. These were not infrequently the main cellular type found in the lumens of newly formed capillaries. The capillary vessels were usually ectatic and varicose. In two thirds of the polyps endothelial granulomas were observed within vessels located in the center or in the pedicle. Vascular changes often coexisted with locally corresponding atrophic alterations in the surface epithelium. In many cases strands of smooth muscle tissue extended through the pedicles into the cores of the polyps and formed there occasionally whirl-like, often hyalinized tufts.

The histologic observations recorded concerning the precancerous lesions (intraepithelial abnormalities, leukoplakia, mucous polyp) demonstrate clearly that the first preparatory cellular response to the contact with the carcinogenic agent occurs in the epithelial lining of the bladder. These epithelial changes may occasionally advance even as far as an early infiltrative malignant lesion before any appreciable reaction of the surrounding vasculoconnective tissue is noticeable. It is this type of lesion which may escape cystoscopic discovery as it may not produce mucosal thickening or be associated with papillary projections or vascular reactions which would attract attention and provide visible evidence.

Chronic inflammatory, obliterative and ectatic vascular and fibrotic changes are apparently secondary and nonspecific. They are present in only part of the lesions and are often accompanied by atrophic epithelial alterations. The frequent formation of endothelial granulomas and the subsequent vascular obliteration may be attributed to three possible causes. As they are most often found in polyps, it appears likely that the topographic distortion connected with the formation of the polyps may exert a twisting or stretching effect on the vessels and thereby elicit endothelial damage and proliferation. Endothelial injury and regenerative proliferation may also result from the resorption of toxic products through the mucosa into the intraepithelial capillaries and thus also may angiectases be caused. There exists, moreover, the possibility that chemospecific allergic reactions are involved in the formation of endothelial granulomas, especially as many of the early lesions show intravascular and extravascular eosinophilia and marked interstitial edema (Hueper, 1936; Pagel; Reuterwall).

The frequency of vascular hyperemia and proliferation, which are observed in the great majority of precancerous reactions, suggests that an increase in the blood supply is an essential preparatory feature of neoplastic cell growth (Paschkis and Bruegel). This conception receives support from various sources. Ewing stated that increased vascularity has been demonstrated in the beginning of many carcinomas and has

been assumed to account for the awakening of many cell rests. Thiessen found in his studies of the relative vascularity of benign and malignant gastric lesions that in an entirely unexpected and, as he felt, paradoxic way the vascularity increased progressively from the simple ulcer to the ulcer with cytoplasia to the ulcer with early malignancy and decreased as the carcinoma became well established. Kreyberg concluded from his experimental investigations of the precancerous changes in the skin of tarred mice that marked local vascular hyperemia accompanies epithelial hyperplasia and in association with other factors may exert a stimulating effect on cellular proliferation. This conception is, moreover, in good agreement with well established experiences in regard to the nutritive influences controlling sustained cell growth (Hueper, 1933; Hueper and others, 1933). The observations made during the study of the early lesions of the bladder do not support, on the other hand, the belief that permanent vascular and circulatory insufficiency and fibrosis are the primary responses and that the neoplastic proliferations develop on the basis of nonspecific abnormalities in the supporting connective tissue (Wohlbach).

Neoplastic Lesions.—"Aniline tumors" may be grouped on pathologic grounds according to the following classification:

1. Papilloma with histologically benign structure
2. Papilloma with histologically benign and malignant component parts
3. Carcinoma
   (*a*) Papillary carcinoma of transitional cell type
   (*b*) Nodular infiltrative carcinoma: transitional cell type; glandular type; anaplastic or sarcomatoid type

1. Histologically benign papilloma. This type is represented by either villous tufts of varying size, composed of slender, delicate, feathery fibroepithelial projections, or by rather plump, thick, warty protrusions possessing a larger amount of usually edematous connective tissue in between the epithelial covering. The papilloma may be connected with the wall of the bladder by a very narrow pedicle, or there may be a broader tissue bridge as connecting link; or numerous small papillary projections (papillomatosis) may extend from the mucosa of the bladder with narrow interspaces. The epithelial lining discloses marked variations in thickness and in cellular character. It may be represented by as little as two or three rows of cells or as many as twenty or more strata of epithelium. In the majority of cases it resembles closely the normal transitional epithelium of the bladder. Occasionally papillomas are found which are covered by closely packed small oval or round hyperchromatic cells of an almost lymphoid character. Others occur

which are lined by large polygonally shaped epithelial cells. Cells of this type may, moreover, be seen in the superficial layers of some of the transitional cell papillomas. Degenerative changes, such as balloon-like swelling, cystoplasmic vesiculation, nuclear pyknosis, atrophic shrinkage and intraepithelial cyst formation (pseudoglandular structures), are not uncommon features, especially in papillomas with thick epithelial lining. The merger of the epithelial covering of adjacent papillae may result in the production of broad solid epithelial sheets. The basal layer of the epithelium is always sharply demarcated from the connective tissue core, even in cases in which there is a moderate degree of irregularity in the morphology and arrangement of the epithelium.

The stroma is usually a loose, edematous and vascular connective tissue varying greatly in amount with the individual tumor. There is often a mild to moderate infiltration of lymphoid and mononuclear cells, containing not infrequently also a varying number of eosinophilic cells. Hemorrhages into the edematous tissue, especially into the tip portions, are often seen. There are occasionally phagocytic cells containing brown granular pigment in the neighborhood of vessels and directly underneath the epithelial lining. The interstitial edema may in rare instances attain such degrees that small central cysts filled with a pink-stained homogeneous matter are formed. These are surrounded by a thin layer of connective tissue with a few capillaries, which in turn is covered by the epithelial lining. Tumors of this type have the appearance of a bunch of grapes.

There is present in general a rich capillary network. The vessels are usually dilated and hyperemic. The epithelial covering is not infrequently in direct contact with the endothelial lining. The capillary structures are sometimes so dense and dilated that the neoplasm has more the appearance of a papillary hemangioepithelioma. Degenerative changes in the vascular walls occur often. There may be hyaline thickening or calcium incrustation of the walls of these delicate vessels. Concentric endothelial thickening of precapillary vessels and endothelial granulomas, sometimes associated with fibrosis and hyalinization of the pedicle, are not uncommon.

2. Papilloma with benign and malignant components. This type exhibits a general pattern very similar to that just discussed. But side by side with the benign epithelium there occur, scattered throughout the epithelial coat, complexes of irregularly arranged and shaped cells, sometimes of large cellular and nuclear size. Mitotic figures are frequent and often irregular. Such foci may remain within the limits of the epithelial lining, or they may exhibit invasive properties, penetrating into the core and its vessels and through the pedicle into the base and underneath the adjacent mucosa. This development occurs the more

readily as the focal transformations with active malignant qualities are usually located near the base of the tumor, in contrast to those found in mucous polyps, in which they usually occupy the tip portions. The scattered distribution of these foci and the demonstrated transitional phases strongly suggest that papillomas with benign and malignant epithelial components are primarily benign neoplasms.

3. Carcinoma: (*a*) Papillary carcinoma is composed of rather bulky papillary projections lined by numerous layers of irregularly shaped and sized transitional epithelial cells, which cells, arranged in disorderly fashion, invade diffusely the loose and vascular connective tissue of the cores of the papillae and the bladder wall surrounding their base. Usually the tumor arises from a broad base, suggesting that papillary leukoplakia may represent the preceding condition. Normal and pathologic mitoses are frequent in the epithelial strands. Giant cells with several nuclei, areas with polygonal cells and cornification, balloon-like swollen cells, pseudoglandular formations and other abnormalities may occur. The epithelial cells invading the connective tissue are sometimes arranged in garland formation. The structural characteristics of the stroma do not vary from those of the previously described type, but inflammatory reactions appear to be more frequent and pronounced in the frankly carcinomatous variety.

(*b*) Nodular infiltrative carcinoma originates either from a leukoplakic area or from epithelium showing merely atypical structure and arrangement of cells. In both instances epithelial cell strands and groups invade infiltratively the submucosa, which often shows during more advanced stages a more or less dense lymphoid infiltration and increased vascularity. The tumor cells may vary markedly in type and arrangement. In the majority of tumors of this type there is a definite resemblance to transitional epithelial cells. The cells grow in rather large, well circumscribed pegs. In other instances the cells are larger and paler staining and show a tendency to undergo liquefaction necrosis, thus producing pseudoglandular and pseudocystoglandular formations, which give the tumor an adenoid appearance. Spinous cell tumors are rare.

Neoplasms with true glandular structure are exceptional. They are usually composed of infiltratively growing tubules lined with high cuboid, low stratified hyperchromatic epithelium. More immature forms are still less frequent.

There occur also tumors of a completely undifferentiated type. The cells are round or oval and grow in large ill defined masses, which are diffusely infiltrative. Tumors of this type have often a sarcomatoid appearance.

The malignant tumors observed occasionally in kidneys and renal pelves are of either papillary or large nodular structure and usually destroy large parts of the involved kidneys. They metastasize readily and are often very anaplastic.

Among the specimens obtained from human bladders, one of adenocarcinoma of the prostate gland and one of dysontogenetic tumor of the floor of the bladder were included. While Oppenheimer (1926 [*c* and *d*]) considered the possibility that carcinoma of the prostate also might result from exposure to aromatic amines, Engel (1937) recently pointed out that such an assumption is unjustified, because carcinoma of the prostate is not more frequent among dye workers than in the general population.

An occupational etiologic relation of the dysontogenic tumor could be construed only if activation of an embryonic tissue anlage by the occupational carcinogenic agent is assumed. This appears to be highly unlikely.

The various lesions described were numerically distributed among the 125 human specimens studied in the following manner: chronic cystitis in 2; mucous polyps in 8; leukoplakia plus papilloma in 1; papilloma in 34; papilloma plus carcinoma in 10; papillary carcinoma in 23; solid, nodular carcinoma in 33; adenocarcinoma in 1; carcinoma of the renal pelvis in 1; dysontogenic tumor in 1; prostatic carcinoma in 1. The histologic grades of malignancy were recorded in 54 cases of carcinoma (cases of papilloma were not included, as this tumor was considered as histologically benign): Seven were of grade I, 23 of grade II, 19 of grade III, and 5 of grade IV. The low incidence of adenocarcinoma among aniline tumors agrees well with that generally found—2 per cent (Matthews).

PATHOLOGIC RELATIONS

The ratio of benign to malignant aniline tumors is, according to Büttner, 1:3. Gay calculated for a series of 124 tumors from various German sources a ratio of 1:2 and found a similar ratio in his first American series of 23 cases. In his latest communication, dealing with 61 cases, he has changed the ratio to 1:1. He attributed this discrepancy to the earlier discovery of the tumors in the American workers, on account of the routine practice of cystoscopy, and saw in the observation supportive evidence for his contention that there is a transition from benign to malignant lesions with the passage of time. The comparative figures for tumors of unknown cause are: Joseph (1931), 34.3 per cent papilloma and 65.7 per cent carcinoma; Voelcker and Boenninghaus, 76 per cent malignant tumors among 1,472 epithelial

neoplasms of the bladder; American Urological Association Registry, 19.5 per cent benign lesions among 851 tumors.

The biologic behavior of the aniline tumors varies considerably, depending to a certain extent on their histologic structure. Benign villous papilloma may remain stationary or show only progressive local growth for many years, without producing symptoms except those of recurrent hemorrhages, which may, however, be very severe. It may, on the other hand, become rapidly malignant, especially following incomplete removal. Suddenness of appearance and occasionally astonishing rapidity of growth may be observed with benign as well as with malignant lesions.

It is generally asserted that bladder tumors, regardless of etiology, metastasize late if at all (Hueckel). Simon (1932) even stated that aniline tumors, while histologically identical with bladder tumors of unknown genesis, are biologically more benign than the latter, as in 81 cases he did not observe in vivo or at autopsy any metastatic deposits. His optimism is not shared, however, by Mueller (1936), who pointed out that according to the observations made in the Basel district aniline tumors are extraordinarily malignant and frequently and readily form distant metastases. An analysis of 17 cases of aniline tumor on which sufficiently detailed autopsy records are recorded in the literature of Europe showed that distant metastases were present in 8. In none of the 5 American cases in which autopsy was made were metastases found (Gay). In 3 instances, however, there was primary carcinoma in other organs (skin, pancreas, kidney). The explanation of the apparently fundamentally different behavior of aniline tumors in different regions and different industrial plants is not evident. Experiences with experimental tar and dibenzanthracene tumors suggest that such differences may be attributable to marked variations in the degree and length of exposure to the carcinogenic agent. It is a well known fact that the number of malignant tumors and the appearance of metastases depend to a certain extent on these factors, and a massive exposure to a carcinogenic agent may cause the development of neoplasms in usually less exposed organs.

Multiplicity is as frequent among bladder tumors having their origin in exposure to aromatic amines as among those of unknown genesis (for the latter Albarran gives the frequency of multiplicity as 25 per cent). The relation for aniline tumors is demonstrated in the following analysis of 98 instances reported in the literature.

	Papilloma	Carcinoma	Total
Single	21	57	78
Multiple	3	17	20

Washburn with 63 cases listed 24 as multiple and 39 as single.

Benign and malignant tumors may coexist in the same bladder, and multiple neoplasms of the same biologic type (malignant or benign) may show marked difference in histologic structure (Wendel; Oppenheimer (1920 [b] and 1926 [a]; Gay). This marked variation in histologic structure of multiple neoplasms in a particular bladder was especially impressive in dogs treated with betanaphthylamine (Hueper, Wiley and Wolfe). Among 50 or more lesions present at one time practically all types of preneoplastic and neoplastic conditions were found. This factor in addition to the histologic evidence of multiple intraepithelial lesions is sufficient proof that the multiplicity of aniline tumors is primary and not caused by secondary mucosal extensions from one tumor. Examination of the mucosa of the bladder in dogs with general papillomatosis frequently showed near the base of well developed tumors small foci of irregular and atypical epithelium which were entirely unrelated to the neoplastic formation but which represented minute preneoplastic lesions.

LOCALIZATION AND THE DEVELOPMENTAL MECHANISM

In spite of the fact that carcinogenic aromatic amines or their organic conversion products circulate in the blood, tumors are formed almost exclusively in the bladder, rarely in any other part of the urogenic tract (kidney, renal pelvis, ureter) (Rehn, 1906; Marchand; Sebening; Leuenberger; Oppenheimer, 1926 [d]; Mueller, 1936; Gay) and, as far as is known, never in the skin or in the digestive and respiratory organs, which are the sites of the most massive and direct primary contact and the ports of entrance of the aromatic amines to the organism. Theoretically there are two ways by which the urinary epithelium of the bladder and the other parts of the urinary tract may come in contact with the carcinogenic agent. The carcinogen circulating in the blood may escape from the terminal capillaries into the mucosa and thus enter the epithelial cells—either directly or, after release into the content of the bladder, by resorption. The second possibility is that the carcinogen, possibly produced from the original substances by metabolic action of the liver or of the kidneys, is excreted with the urine into the bladder and can then act on the mucosa for a prolonged period, until discharged.

The majority of investigators favor the last-mentioned conception (Oppenheimer; Engel, 1937; Hueper, 1934 [c], and others). It has been pointed out by them that the urine containing the suspected carcinogenic substances passes rather rapidly through the kidney, renal pelvis and ureters and that therefore these organs, as far as time of contact is concerned, are less exposed than the bladder, where the urine collects and remains for some time. In addition to the prolonged

exposure of the wall of the bladder is the presence in the bladder of an increased amount of the carcinogenic agent, depending on the quality of urine contained in the lumen. It may be contended that this factor might be made of importance by assuming that the concentration of the carcinogenic substances must reach a certain upper limit before a proliferative response is elicited; the same argument has been applied with reference to the concentration of aromatic amines in the blood to explain the absence of aniline tumors in other organs. Oppenheimer suggested that the carcinogenic substances are possibly precipitated from the urine on the wall of the bladder and act thereby directly on the mucosa. This conception may possess a certain merit, as the solubility of the urinary metabolites of the aromatic amines depends on the reaction of the urine, becoming progressively lower with increasing alkalinity of the urine. Precipitates thus formed would settle and collect on the floor of the bladder, i. e., the place where in man the majority of bladder tumors are situated. It may be mentioned in this connection that the reaction of the urine in the dogs with experimental bladder tumors (Hueper, Wiley and Wolfe) became definitely and at times strongly alkaline, though normally acid, many months before the tumors became manifest. Mention may also be made of the reactive urinary conditions apparently existing in cases of the other occupational cancer of the bladder, the bilharzial cancer. Hoffmann quoted Dolbey and Moore in this matter as follows:

> The incidence of cancer in relation to Bilharzia suggests that only in an alkaline infected medium such as the stagnant urine of cystitis in Bilharzia bladders does the irritation of ova produce cancerous changes. In the renal pelvis, the ureter and the intestinal canal the incidence of parasitic disease is almost as great as in the bladder, and yet the development of cancer is almost unknown.

Kennaway considered the possibility that the potentially carcinogenic substance acquires cancer-producing qualities first under the chemical conditions which prevail in the urine. Since this change takes place rather slowly, the kidneys and ureters should tend to escape.

If these considerations are applied, additional support for the urogenous theory is obtained from the interrelations existing between the local distribution of the aniline tumors in the bladder and the anatomic conditions of the viscus, especially those of the floor. Aniline tumors in man are most frequently found in the trigonal and paratrigonal area and the lower posterior wall, i. e., in the dependent parts of the organ. Hueper (1934 [c]) found 60 of 81 tumors and Gay 11 of 17 tumors located in the region of the floor. A more detailed analysis of the distribution shows that there is crowding of tumors around the ureteral and urethral orifices, where a certain mechanical trauma from the urinary flow is present, and in the areas lateral from the plicae

uretericae and in the fossa retroureterica, which represent the most dependent parts of the floor, as the area of the trigon is slightly elevated.

	Papilloma	Carcinoma	Total
Trigonal region	13	47	60
Elsewhere	2	19	21
Mixed (multiple tumors).....		8	8

The marked significance of static conditions for the localization of the aniline tumors in the bladder has been recently emphasized further by observations made in dogs with experimental tumors (Hueper, Wiley and Wolfe). These investigators found that the great majority of the pretumorous and tumorous formations were located in the region of the dome and of the adjacent and mainly anterior parts of the bladder, where also the largest tumors were noted. On account of the different static conditions present in the dog, these parts represent the most dependent parts of this viscus when the dog is in a lying or a standing position. The normal differences in the density of vascularization between the floor and the dome of the bladder are therefore not the controlling factor in this respect, as claimed by Ferguson (1934 and 1937).

The importance of local urinary conditions in the localization of aniline tumors is demonstrated further by observations of Sebening, Mueller (1936) and Gay, who reported the occurrence of tumors in renal pelves in association with anatomic anomalies of the corresponding ureters which interfered with the free flow of urine through these conduits. A status of prolonged urinary retention and mucosal contact within the affected area was thus produced similar to that existing normally in the bladder. These factors may be considered on the basis of the urogenous theory as predisposing to the development of tumors in the region of the urinary tract situated above the obstruction.

The urogenous theory receives support also from the experimental histologic observations recorded in regard to the sequence of cellular changes in the different layers of the bladder in dogs. The fact that the first cellular reactions developed in the epithelium suggests strongly action through urinary contact.

The hematogenous theory, sponsored by Ferguson and Gay, assumes that the carcinogenic agents circulating in the blood have a special affinity for the bladder tissue, causing there specific primary injury to the terminal capillaries of the submucosa of the bladder and other parts of the urinary tract. The validity of this hypothesis is supported, according to its authors, by the following evidence: 1. The majority of the aniline tumors occur in the lower half of the bladder, i. e., in the best vascularized part of the viscus, but do not involve most often its most dependent part, the trigonal area. 2. Aniline tumors develop

not only in the bladder but also in the kidneys, renal pelves and ureters, indicating thereby a systemic and not merely a local organic affinity. 3. Histologic examination of early lesions of the human bladder demonstrates that the vascular changes precede the epithelial reactions, which originate in the basal layer. 4. The mucosa in the vicinity of bladder tumors of occupational and nonoccupational origin does not not show on microscopic study any sign of irritation, such as hyperplasia, which can be expected if action is through urinary contact. 5. Attempts to demonstrate a carcinogenic substance in the urine of persons with occupational and nonoccupational tumors have failed. 6. The urinary excretory metabolites of aromatic amines have been proved to be carcinogenically inert. 7. The assumption that there is an exclusive chemical tissue specificity in the causation of bladder tumors is not unique, as a similar hematogenous mechanism is claimed to be present in the causation of arsenical cancers, the occurrence of which is restricted to the skin.

The hematogenous theory is an interesting conception which deserves further investigation, especially with experimental methods. Ferguson proposed to this end to transplant the ureters of an animal into the rectum and to exclude thus the bladder mucosa from any contact with urine, leaving only the possibility of hematogenous action. A positive outcome of such an experiment, i. e., the formation of bladder tumors, would greatly support the hematogenous theory. But a negative result would not entirely disprove it, as one might argue that the marked impairment of the circulation of the blood in the functionally inactive bladder might have influenced its reactivity. Hueper suggested therefore that one or both ureters of the female dog be explanted to the uterine horns or to a rectal pouch serving as an artificial bladder and that a sigmoidostomy be done to take care of the fecal eliminations. The appearance of tumors in the uterus or in the rectal "bladder" would indicate that the urine contained carcinogenic agents.

The factual evidence available at the present time lends little support to the hematogenous conception. Many of the serious objections which may be raised against its validity are contained in the discussion of the data favoring the urogenic origin of aniline tumors. They do not need to be repeated. There are, however, a few points which may be worth considering in this connection.

The hematogenous theory assumes actually the presence of a twofold affinity: a primary purely chemical one of the terminal capillaries in the submucosa only, exempting the elements of the second vascular network located in the muscularis, and a secondary carcinogenic epithelial affinity, leaving the primarily involved mesenchymal elements unaffected, as so far practically none of the aniline tumors has been

of a sarcomatous type. Such a selective behavior of a chemical carcinogen, which cannot be accounted for by any known special chemical secretory or excretory qualities of the bladder mucosa, must appear extraordinary in view of the well established faculty of the various synthetic carcinogenic chemicals to elicit carcinomatous as well as sarcomatous responses, depending mainly on the type of tissue with which immediate contact occurs. A comparison with arsenical carcinoma is scarcely justified, for not only does the skin possess a known chemical affinity for arsenic and therefore stores it and excretes it with the sulfur-containing compounds contained in keratin and hairs, but arsenic causes a fundamental disturbance in the distribution and production of melanin.

Reference must be made to some observations made by Schär which were recently mentioned by Henschen, as they seem to provide some evidence supporting the hematogenous conception. Schär found that naphthylamine is released from the vessels of the bladder, accumulating in the form of granules in the perivascular tissue. While the interpretation of these findings is difficult on account of the absence of detailed experimental data, some preliminary investigative work on similar lines conducted by me several years ago may help to elucidate these observations. The purpose of the experiments was to attempt to demonstrate betanaphthylamine in the tissues with the help of color reactions.

Nitroaniline diazotized by the addition of a small amount of sodium nitrite was used as a reagent, since a watery solution of this compound (10 per cent nitroaniline plus a few drops of a 5 per cent solution of sodium nitrite) gives, when coming in contact with even very small amounts of betanaphthylamine, an intensely cerise red precipitate.

Mice which had been given subcutaneous injections of 0.01 Gm. of betanaphthylamine were opened after from one to two hours while still living. A freshly prepared mixture of the reagent described was dropped on the bladder, liver, kidney and finally the lungs. The organs were studied with a Zeiss epicondenser under direct reflected light. Accumulations of reddish granules were seen in the superficial cells of the liver (hepatic cells and Kupffer cells) and of the kidney (tubular epithelium and lumens). When this reagent was injected directly into the bladder filled with brown urine a heavy red precipitate was formed. Following intracardial injections of the reagent, orange-red granular deposits were visualized in the wall of the bladder, especially in the lumens and perivascular tissue of blood vessels. The epithelium of the bladder appeared to be without colored matter, except some cells with fine, dustlike red-brown granules located in their cytoplasm. These observations were substantiated on unstained frozen sections prepared from unfixed tissue with the cooled knife method (Hueper, 1934 [a]).

A second series of mice, which were given subcutaneous injections of 0.002 Gm. of betanaphthylamine hydrochloride three times at four day intervals, were killed in pairs three, five and ten days after the last injection. None of the organs tested showed any color reaction grossly or microscopically. The retroperitoneal and perivesical fat tissue gave, three days after the last injection, an orange-red color when the reagent was dropped on it. A faintly positive reaction was obtained up to five days after the injection.

The observations reported indicate that intravascular and perivascular precipitations of betanaphythlamine are apparently the result of an acute toxic effect when the organism is flooded with this substance. On the other hand, it was quite evident that the urine not only contained a higher amount of the aromatic amine but continued to show it in demonstrable traces for a longer period than any of the parenchymatous organs tested. It is therefore reasonable to assume that under ordinary metatoxic conditions of exposure the main and probably only contact of the epithelium of the bladder with the carcinogenic agent takes place on the mucosal surface.

It appears premature to attach definite significance to the failure to demonstrate carcinogenic substances in the urine of persons with bladder tumors. The technical methods used for chemical extraction and experimental testing were doubtlessly inadequate for this task.

The present state of knowledge also does not permit any final statement in regard to the potential carcinogenic qualities of the urinary metabolites of aromatic amines, as only some of them are actually known and definitely identified, while none of them has yet been reliably tested for carcinogenic properties. Some time ago I made experiments with an impure 2-amino-l-naphthol, one of the known urinary excretory products from betanaphthylamine. Concentrated solutions of this substance in olive oil and rabbit serum, respectively, were injected intraperitoneally into white mice of common stock in individual doses of 0.1 cc. twice weekly for a period of approximately six months. There were 25 animals in each series. Histologic examinations were made of 36 mice. The following neoplastic formations were found in this group: retothelial sarcoma in 3, myeloid leukemia in 1, pulmonary adenoma in 5, splenic hemangioma in 1 and sebaceous gland adenoma in 1. While the evidence presented is suggestive that the tumorous conditions are at least in part attributable to the treatment given, it is far from conclusive.

The predominant location of bladder tumors in the region of the bladder floor has been ascribed also to embryonic developmental disturbances, which frequently involve this area and cause the production of tissue malformations and misplacements. These cell complexes represent, according to the Cohnheim-Ribbert theory, a tissue predisposed to the formation of tumors. The experimental observations which I made in dogs concerning the numerous minute foci of atypical epithelial proliferations and the local shift of the canine tumors toward the dome demonstrate definitely that the conception of Cohnheim as to the genesis of tumors has no place in the explanation of the causative mechanism of aniline tumors.

The trigonal prevalence and causation of aniline tumors have been related also to the chronic inflammatory processes which frequently

occur in this part of the bladder, on the assumption that exposure to aromatic amines results in chronic cystitis. The further course of events is then readily explainable by the application of Virchow's theory of chronic irritation. The histologic observations which I made on dogs and those reported by Perlmann and Staehler (1932 and 1933) on rabbits indicate that Virchow's theory cannot be applied to aniline tumors. Whenever chronic inflammatory changes were present in association with preneoplastic or neoplastic lesions they were secondary and coincidental but not causative. In consideration of the absence of tumor formation in the great majority of cases of chronic chemical occupational dermatoses and pulmonary conditions, chronic nonspecific irritation appears to be highly overrated as a carcinogenic factor (Oppenheim). Aniline tumors are not phenomena of secondary epithelial growth on the basis of a chronically inflamed and impaired supporting tissue. Neither symptomatic nor morphologic evidence supports such a conception.

TREATMENT

It may suffice here to state that the indications for therapy and the methods used in the management of aniline tumors are identical with those for bladder tumors in general. Surgical excision, electrocoagulation, irradiation with roentgen rays and treatment with radium emanation have been employed. According to the experiences of Simon (1932), Mueller (1936), Ferguson (1937) and Washburn, these tumors respond to irradiation. Mueller stated, however, that the metastatic tumors react more readily to this therapy than the primary growths in the bladder. In view of the frequent multiplicity of aniline tumors, therapeutic measures which affect the entire viscus without causing functional impairment deserve special consideration.

A new and still experimental method of therapeutic attack has been proposed by Henschen. Following the thoughts of Bauer in regard to the therapeutic effect of the application of minute amounts of 3,4-benzpyrene to skin cancers, Henschen has administered during the last two years to his patients with bladder tumors small amounts of naphthylamine by mouth. He believes that the contact of the naphthylamine with the carcinogenic agent in the wall of the bladder, partially or totally inactivates the carcinogen. The preliminary results obtained with this method are, according to its author, promising.

PROGNOSIS

The final outcome of any neoplastic disease depends on various factors, such as the degree of malignancy (local and metastatic activity of growth), the extent and location of the tumor, the age and general condition of the patient and the type and quality of the therapeutic

procedures. An accurate prognostication of bladder tumors, especially those caused by exposure to aromatic amines, is complicated, moreover, by the fact that recurrences or new growths may appear many years (from fifteen to twenty) after the removal and apparent cure of the first neoplasm. The curative results reported by various authors differ, therefore, considerably. It must be pointed out in this connection that even benign papilloma may prove in the long run fatal on account of its tendency to recur and to bleed sometimes profusely (Engel, 1937). In older statistics the mortality among diseased workers is shown to have been high, especially as concerns aniline cancers, which Leuenberger considered as having an unfavorable prognosis. Oppenheimer recorded the mortality as 73.5 per cent; Schwerin, as 66 per cent. Of Nassauer's 32 patients, 27 are dead; of Büttner's 10 patients, 5 have died; of Leuenberger's 18 patients, 11 have succumbed. But the figures of the two last-mentioned authors are not final, as some of the patients have been observed only a short time, and the ultimate fate of others is unknown. Mueller (1936) stated that 7 of his 36 cancerous patients were still living. The average duration of disease in his fatal cases was two years and a half. Death was often due to an ascending renal infection and urinary sepsis. In all of his cases the tumors proved to be very malignant and ran a rapid course. Metastases in various organs (lymph nodes up to the fossa supraclavicularis and vertebrae, skin, liver, lungs and brain) were present in 13 of 17 persons examined post mortem. Mueller (1931) emphasized the fact that the clinical extent of the tumor in the bladder offers no information about the extravesical distribution of the tumor.

A much more favorable prognosis has recently been given to aniline tumors by Simon (1932). Bladder tumors with their genesis in exposure to aromatic amines run, according to him, a slower course and respond better to the various therapeutic procedures than bladder tumors of unknown origin. He reported three year arrests in 54 per cent and five year arrests in 48 per cent of his 81 cases of aniline carcinoma, whereas there were five year arrests in only 10.5 per cent of his cases of bladder tumors of unknown origin. Similar favorable results were reported by Washburn. Among 86 patients there were 9 deaths, 7 of them directly or indirectly attributable to the neoplasms. Fifty-two (62 per cent) of the patients were tumor-free for varying lengths of time. Washburn ascribed these good results in part to the fact that the tumors were discovered when they were in a rather early stage through the routine practice of cystoscopy. It appears doubtful, however, whether these good results will be permanently maintained, as the workers of this group have returned to the hazardous operation and their bladders are therefore again exposed to the action of the carcinogenic agent. This

may activate any latent preneoplastic mucosal lesion preexisting from the former exposure. Such a course must be expected according to experiences with occupational and experimental tar and pitch tumors. The possibility therefore exists that recurrences may be more frequent in this series than they would be if the exposure had been terminated completely after the discovery of the first tumor.

SUSCEPTIBILITY

In many clinical reports reference is made to an apparent difference in individual susceptibility among workmen in the presence of an identical type and duration of exposure. Some of the variations in personal reactivity are certainly only apparent; i. e., they are referable to differences in cleanliness, working habits and general intelligence. These factors may have an important influence on the amount of exposure received. But, doubtless, some of the discrepancies must be accounted for by an assumption of differences of a personal or constitutional nature. Such variations in neoplastic responsiveness were also evident among the dogs used in the experiments of Hueper, Wiley and Wolfe. While the first dogs presented tumors after twenty months of treatment, 2 were still cystoscopically free from pathologic manifestations after thirty months of exposure. As the microscopic examination of the bladder of one of these dogs showed the presence of a minute carcinomatous lesion, it stands to reason that any degree of personal resistance against chemical tumor formation may ultimately be overcome if the exposure to the aromatic amine is sufficiently long and intense. The high frequency of bladder tumors among certain groups of dye workers confirms this conception.

From the observations so far made in man it may appear as though the male sex only is susceptible to aniline tumors. This has its plausible explanation in the fact that normally only men are employed in these operations. The experimental production of these tumors in female dogs indicates that no difference occurs on sex lines.

Those interested in more detailed information concerning the chemical, technical, medicolegal and social aspects of these occupational tumors are referred to the papers of Nassauer (1920), Hueper (1934 [c]), Gehrmann (1936) and Engel (1937).

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Félix Mesnil, of the Pasteur Institute, Paris, has died at the age of 70 years. He became attached to the Pasteur Institute in 1892 and played an important part in the development of the chemotherapy of diseases of a parasitic nature.

S. B. Wolbach, of the Harvard University Medical School, has been elected a member of the National Academy of Sciences.

Walter Schiller, pathologist at the Jewish Memorial Hospital, New York, has been appointed pathologist at the Cook County Hospital, Chicago, to succeed the late Richard H. Jaffé.

Max Neisser, professor of hygiene and bacteriology at Frankfort on the Main, has died at the age of 69. His name is associated with the deviation of complement (the Neisser-Wechsberg phenomenon).

Benjamin White, bacteriologist and director of the division of biologic laboratories in the Massachusetts Department of Health until his retirement in 1933, has died at the age of 59 years.

James W. Henry has been appointed instructor in pathology at Loyola University, Chicago.

James N. Patterson, assistant professor at the University of Cincinnati, has been appointed director of laboratories of the state department of health at Jacksonville, Fla.

Courtland Y. White, director of the bacteriologic laboratory of the city of Philadelphia and of the pathologic laboratory of the Episcopal Hospital, Philadelphia, died on Jan. 14, 1938, at the age of 64.

Peyton Rous, a member of the Rockefeller Institute for Medical Research, New York, has been elected a member of the Royal Academy of Sciences of Denmark.

A. L. Joyner, assistant in bacteriology and pathology at the Rockefeller Institute for Medical Research, has been appointed assistant professor of bacteriology and pathology at the University of Alabama.

Society News.—The American Society for Experimental Pathology has elected the following officers: Morton McCutcheon, president; Ernest W. Goodpasture, vice president, and Paul R. Cannon, secretary-treasurer.

Katharine Howell has been elected president, S. A. Levinson vice president and Edwin F. Hirsch secretary-treasurer of the Chicago Pathological Society.

The American Public Health Association will hold its sixty-seventh annual meeting in Kansas City, Mo., Oct. 25-28, 1938.

Francis Amory Septennial Prize.—The American Academy of Arts and Sciences, Boston, announces that the first award of this prize is scheduled for 1940. The amount will exceed $10,000 and may be given in one or more awards. The prize is the outcome of a gift by the late Francis Amory and is to be given for outstanding work in the alleviation or cure of disease affecting the human genital organs.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Survival and Revival of Nerve Centers Following Acute Anemia. C. Heymans and others, Arch. Neurol. & Psychiat. **38**:304, 1937.

The problem of anoxemia and acute anemia of the vegetative centers (circulatory and respiratory) has been studied by the authors on isolated heads of dogs and also on intact animals. Their main conclusions are that the vegetative centers are resistant to artificially produced anemia and that they can be revived after the circulation has been entirely cut off for as long as thirty minutes. Some centers are more, others are less, sensitive. Recovery, however, is not complete, for dogs that recovered after an arrest of circulation of thirty minutes' duration usually died within from ten to fifteen hours, in a state of coma, while in animals in which the arrest of circulation was limited to five minutes the recovery of the nerve centers was generally complete.

George B. Hassin.

Effect of Alcohol on Cerebral Vessels. C. B. Thomas, Arch. Neurol. & Psychiat. **38**:321, 1937.

The method of Forbes (measurements of the caliber of the pial arteries through a tight window) was used by Thomas in studies of the effect of alcohol on the cerebral vessels of cats and rabbits. The arterial pressure was recorded from the femoral artery, and the spinal fluid pressure, from the cisterna magna. Alcohol (25 per cent) was injected into the saphenous vein, carotid artery and cisterna magna; it was also given by stomach tube and applied locally beneath the window. Intravenous injection usually gave a prompt slight constriction of the pial artery, followed by pronounced and rapid dilatation, which was maintained for less than thirty seconds. No significant change in the caliber of the pial veins was noticed. Cisternal injection caused a rise in the pressure of the cerebrospinal fluid, with a return to normal within fifty-five seconds, while the arterial pressure showed no changes. Injection of alcohol into the left carotid artery produced constriction of the pial artery, followed by immediate dilatation, which in some instances lasted one hour and fifteen minutes. Administration of alcohol by stomach tube in anesthetized animals caused no dilatation of the pial arteries, and the arterial as well as the cisternal pressures remained unchanged. In an unanesthetized animal there was slow, steady dilatation for two minutes. Some of the conclusions arrived at by Thomas are that alcohol invariably produces a rise in the cerebrospinal fluid pressure and increases the flow of blood through the brain and that dilatation obtains not only in the pial arteries but also in other cerebral arteries and arterioles of the brain.

George B. Hassin.

Relaxin a Principle of [Corpus Luteum] in Human Serum as a Test of Pregnancy. D. Abramson, E. Hurwitt and G. Lesnick, Surg., Gynec. & Obst. **65**:335, 1937.

A substance elaborated by the corpora lutea of guinea pigs, causing relaxation of the pelvic ligaments, was first identified by Hisaw in 1929 and by him termed relaxin. More recently Abramson, in a roentgenographic and clinical study, showed that relaxation of the pelvic joints occurs in pregnant women. This observation has been confirmed by several other investigators. It is generally agreed that relaxation of the pelvic joints is a normal occurrence during pregnancy and that it is demonstrable by roentgenogram so early in pregnancy that any mechanical cause for it is unlikely. The authors have demonstrated in the corpora

lutea of sows and in the serum of pregnant rabbits a principle which is capable of causing symphysial relaxation in guinea pigs during normal or artificial estrus. While slight to moderate degrees of relaxation can be produced in guinea pigs by large doses of theelin, the separation is greatly increased by a small additional dose of relaxin, indicating that the relaxation is not solely a theelin effect, but a synergistic action between theelin and relaxin. A procedure was developed for concentrating blood serum taken from women in the first half of pregnancy which acted on guinea pigs in a manner similar to that of relaxin. Serum from a woman in the eighth month of pregnancy, from nonpregnant women and from a man proved ineffective. It is concluded from this evidence that pelvic relaxation during pregnancy is facilitated by, or at least in part is due to, the relaxin in the human being as well as in many other mammalia. As a routine test for pregnancy the procedure is not considered practicable.

WARREN C. HUNTER.

EFFECT OF THE MEDIUM ON THE AMEBOID MOTION OF NEUTROPHILIC LEUKOCYTES. I. WALLGREN, Arb. a. d. path. Inst. d. Univ. Helsingfors **9**:531, 1936.

When a drop of blood was spread between a slide and a cover slide, placed on a heated stage and watched with a dark field illuminator, there was no motion for about one-half hour, but after that marked ameboid motion began, which assumed different forms. Wallgren found that fresh serum and red blood cells had a stimulating influence on ameboid motion, but that they must be together to exert the optimal effect; old serum interfered with ameboid motion.

I. DAVIDSOHN.

PRODUCTION OF HYPERPYREXIA IN LABORATORY ANIMALS AND IN MAN. K. HUNDESHAGEN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **90**:287, 1937.

Hyperpyrexia was obtained with intravenous and intramuscular injections of a bacterial preparation which Hundeshagen calls pyrifer, the proprietary name, without stating anything about its composition. Judging from the references, one concludes that it must be widely employed in Germany. Hundeshagen describes his experiences with the use of this preparation in rabbits, guinea pigs, rats and mice and quotes the experiences of others with the use of it in dogs, horses, cows and geese. By proper combinations of intravenous and intramuscular therapy, the duration of the fever may be extended. The characteristic blood changes are: marked leukocytosis with a shift to the left, lymphopenia and disappearance of eosinophils, lowering of the alkali reserve, hyperglycemia and hypercholesteremia, followed by leukopenia, shift to the right and relative lymphocytosis. A few observations in man following intramuscular injections of pyrifer are mentioned.

I. DAVIDSOHN.

INVESTIGATIONS OF REFECTION. M. NATHAN, Acta path. et microbiol. Scandinav. **14**:383, 1937.

Nathan supports the theory that in deficiency or lack of vitamin B rats usually lose the power to digest starch, the accumulation of which in the lower parts of the intestine favors growth of the bacteria that produce vitamin B, whereupon the symptoms of vitamin B deficiency disappear and the rat thrives; that is to say, refection takes place.

Pathologic Anatomy

POSTMORTEM ELASTICITY OF THE AORTA IN THE HUMAN ADULT. S. L. WILENS, Am. J. Path. **13**:811, 1937.

The postmortem elasticity of the aorta as measured by the ability of excised portions to retract following extension is a constant and durable property, which varies only with age. In the young adult the elasticity is approximately equal

in all areas and in both transverse and longitudinal directions. With advancing age there is progressive loss of elasticity, which varies in degree in different areas but proceeds at a constant rate for a given area and affects all persons to approximately the same extent. This reduction in elasticity is associated with a failure on the part of the individual elastic fibers to recoil and assume a wavy appearance on relaxation and is commensurate with the enlargement of the vessel as a whole. Reduction in elasticity occurs first and proceeds more rapidly in those areas that are most rigidly attached in situ and in the longitudinal plane. Such areas are presumably capable of less movement with each pulsation during life. The development of intimal plaques is not directly related to this loss of elasticity. A greatly thickened intima can restrict the elasticity of the media to some extent. Loss of elasticity of the media proceeds as rapidly in those subjects in whom slight intimal atheromas develop as in those who exhibit profound changes. The earliest and largest intimal accumulations of lipoid material appear in those areas that are subject to the earliest and most marked loss of elasticity. A hypothesis is advanced to account for this coincidence. It is based on the assumption that lipoid material does not necessarily remain at its point of entrance into the intima but may be influenced by the movements of the vessel during life to lodge in the least elastic and least movable portions. Loss of elasticity with age occurs constantly in an artery, the pulmonary one, not usually the seat of intimal plaques.

FROM AUTHOR'S SUMMARY.

HYPERPLASIA AND REGENERATION OF THE MYOCARDIUM IN CHILDREN. H. E. MACMAHON, Am. J. Path. **13**:845, 1937.

Evidence is presented in the form of mitotic division of the nuclei of heart muscle fibers to indicate, first, that in cardiac hypertrophy in infants proliferation of heart muscle fibers can take place, and second, that in severe myocardial injury in children regeneration of myocardial elements can occur.

FROM AUTHOR'S SUMMARY.

MORPHOLOGIC CHANGES IN THE SUPERIOR VENA CAVA AND RIGHT AURICLE IN RHEUMATIC HEART DISEASE. E. WAALER, Am. J. Path. **13**:855, 1937.

In a study of the superior vena cava at its entrance into the right auricle rheumatic lesions were found in 8 of 73 cases of rheumatic carditis. The inflammatory reactions in the media and adventitia were similar to those seen in the auriculitis and aortitis of rheumatic origin. In 8 additional cases hyaline plaques were found. It could not be decided whether these plaques represented the final, healed stage of acute rheumatic lesions or whether they were sclerotic in nature and due to long-standing cardiac disease.

FROM AUTHOR'S SUMMARY.

PATHOLOGY OF INGUINAL GRANULOMA. R. D'AUNOY and E. VON HAAM, Am. J. Path. **14**:39, 1938.

The pathologic process in inguinal granuloma has been studied in a series of 294 cases observed over five years at the State Charity Hospital of Louisiana, at New Orleans. The typical manifestations of the disease embrace nodular lesions and serpiginous ulcerations, which have a tendency to spread along the moist folds of the pudendal region, healing with the formation of atrophic scars. Atypical manifestations are produced by an unexplained increase in fibroblastic reaction of the host leading to hypertrophic and cicatricial (keloid-like) lesions, which must be considered active stages of the infection. Secondary infection produces serious ulcerative necrotic lesions, which may severely mutilate the infected parts and give rise to sepsis and toxemia. Histologic study of biopsy material and of tissue obtained at autopsy reveals that the stage of infiltration is quickly followed by the stage of granulation, during which the epithelial lining of the skin or of the mucous membrane is perforated by vascular granulation tissue. Leishman-Donovan

bodies can be demonstrated in the infected tissue during all stages of the infection. Search for a causal agent has resulted in the isolation of an organism belonging to the Klebsiella group. Inoculation of various laboratory animals with this organism has failed to produce lesions comparable to the disease in man, although such lesions have been reported as produced by inoculation of material derived from human beings with this disease.

FROM AUTHORS' SUMMARY.

PATHOLOGIC CHANGES IN THE PLACENTA ASSOCIATED WITH ERYTHROBLASTOSIS OF THE FETUS. L. M. HELLMAN and A. T. HERTIG, Am. J. Path. **14**:111, 1938.

Observations on 16 placentas of infants with erythroblastosis of the hydropic variety and on 7 of infants with erythroblastosis of the icterus gravis variety are presented. Pathologic changes in the epithelium, stroma and vascular tree are described which constitute a pathologic syndrome pathognomonic of erythroblastosis of the hydropic variety. Similar but less advanced changes are present in placentas of infants with erythroblastosis of the icterus gravis variety. These changes resemble to some extent those seen in immature placentas and in the epithelium from hydatid moles and in that from chorionepithelioma. In the experience of Hellman and Hertig no other disease of the fetus produces a similar picture in the placenta.

FROM AUTHORS' SUMMARY.

Pathologic Chemistry and Physics

THE CHEMISTRY OF URINE IN THE DIAGNOSIS OF EMBRYONAL TUMORS. S. E. OWEN, Q. G. POLANCO and L. H. PRINCE, Am. J. Cancer **31**:613, 1937.

A qualitative chemical test for the urinary gonadotropic substances is presented. Of 44 cases of teratoma testis in which assays for the urinary gonadotropic substances were positive, the chemical test was positive in 39. Of 26 instances in which gonadotropic substances amounted to 400 or more mouse units per liter, the chemical test was positive in 25. The chemical test was positive in all the 11 urines of pregnant women examined as controls. By the preparation of special extracts of urine, many substances which interfere with the test are eliminated, and the reacting endocrine substances are concentrated. It is believed that the test presented is suitable as a qualitative diagnostic aid in cases of teratoma testis.

FROM AUTHORS' SUMMARY.

OCCURRENCE OF NONHEMOGLOBIN IRON IN WHOLE BLOOD. H. W. JOSEPHS and P. WINOCUR, Bull. Johns Hopkins Hosp. **61**:75, 1937.

Josephs and Winocur found that normally the total iron of the blood corresponds with that calculated from hemoglobin within a limit of ± 6 mg. per hundred cubic centimeters. Under certain conditions the total iron was found to exceed the hemoglobin iron by more than 6 mg. per hundred cubic centimeters. These conditions were: (1) infancy, up to the first two months of life; (2) during iron therapy up to the end of the second year of life; (3) during infections. In addition, an increase in nonhemoglobin iron was found in a few conditions in isolated cases (scurvy, 1 case; lead poisoning, 1 case; myxedema, 1 case; cirrhosis of the liver, 1 case). As pointed out by Starkenstein and others, iron exists in the red cells in a combination from which it can be easily split by hydrochloric acid. This form probably accounts for most of the nonhemoglobin iron occurring normally, amounting to between 1 and 2 mg. per hundred cubic centimeters. It is, however, not increased with increase in the total iron in the conditions named, so that in these conditions iron exists in a so-called "organic form." Its significance is not clear. Two possible interpretations may be advanced: 1. It represents possibly a more primitive form of hemoglobin, having a higher content of iron

than is present ordinarily. 2. It represents an iron-containing organic compound which does not carry oxygen, and it may possibly represent an intermediate product in the formation and breaking down of hemoglobin.

FROM AUTHORS' SUMMARY.

THE ELIMINATION OF SELENIUM AND ITS DISTRIBUTION IN THE TISSUES. M. I. SMITH, B. B. WESTFALL and E. F. STOHLMAN JR., Pub. Health Rep. **52**:1171, 1937.

The urinary and fecal excretion of selenium in cats receiving graded doses of selenium as sodium selenite over periods of from two weeks to six months has been studied. From 50 to 80 per cent of the total intake is usually excreted in the urine, and from a trace to 18 per cent is excreted in the feces. More is excreted in the feces when the selenium is given orally than when it is given subcutaneously. A fairly definite relationship has been found between the concentration of selenium in the urine and the daily dose administered in chronic selenium poisoning. This seems to furnish a basis for estimating the amount of selenium absorbed by man in chronic poisoning. In chronic poisoning with inorganic selenium the element is widely distributed throughout the body tissues, being found in highest concentrations in the liver, kidneys, spleen, pancreas, heart and lungs. In the blood there is more selenium in the erythrocytes than in the plasma. In chronic poisoning with small doses of inorganic selenium the bulk of stored selenium is eliminated within two weeks after the administration of the element is discontinued. Small amounts persist in the urine and in some of the tissues, especially the liver, for a month and possibly longer. The bearing of these findings on the problem of the selenium hazard for man is discussed.

FROM AUTHORS' SUMMARY.

THE DISTRIBUTION OF IRON IN BLOOD. C. E. JENKINS and M. L. THOMSON, Brit. J. Exper. Path. **18**:175, 1937.

A colorimetric method of determining the distribution of iron in blood is described. It is shown that the total iron in blood is greater than can be accounted for by any known method of estimating the concentration of hemoglobin. The observations of Barkan, confirmed by Winegarden and Borsook, are now further confirmed. The nonhemoglobin cellular iron normally amounts to about 7 per cent. The plasma iron amounts to about 0.3 mg. per hundred cubic centimeters of whole blood in males and to about 0.8 mg. in young women. Preliminary work shows that in the anemias the values for nonhemoglobin cellular iron and plasma iron differ largely and significantly from the normal. The estimation of whole blood iron as a means of calculating the concentration of hemoglobin is valueless, and the instances of apparent agreement are due to large errors in the methods of determining the concentration of hemoglobin. FROM AUTHORS' SUMMARY.

RED CELL CHARACTERISTICS IN ACHOLURIC JAUNDICE. J. M. VAUGHAN, J. Path. & Bact. **45**:561, 1937.

Increased fragility of red cells in sodium chloride solutions was found in 35 cases of acholuric jaundice and increased spherocytosis in 25 of 27 cases studied. Megalospherocytosis as well as microspherocytosis may occur in acholuric jaundice. Following splenectomy, increased fragility invariably persisted; spherocytosis was lost in 50 per cent of the patients. It is suggested, therefore, that both erythropoiesis and splenic function are at fault in this disease. A high degree of correlation was found between mean corpuscular thickness and median corpuscular fragility, both in acholuric jaundice and in other conditions before splenectomy. Since fragility remained abnormal after splenectomy while spherocytosis returned to normal, it is concluded that increased spherocytosis is not the fundamental abnormality present in the acholuric red cell. FROM AUTHOR'S CONCLUSIONS.

THE URINARY EXCRETION OF PNEUMOCOCCUS POLYSACCHARIDE IN LOBAR PNEUMONIA. R. CRUICKSHANK, J. Path. & Bact. **46**:67, 1938.

The specific polysaccharides of pneumococcus types, I, II and III are excreted in the urine of the majority of patients with lobar pneumonia due to these three types and may be demonstrated by a precipitation reaction. This urinary precipitation test has only a limited value as a method for the early serologic typing of lobar pneumonia, as the first specimens of urine examined were positive in only one fifth of the type I and one half of the type II infections. The detection of the polysaccharide in the urine early in the infection has, however, a grave prognostic significance, since the mortality in such patients was around 40 per cent, whereas, of those whose urinary specimens were persistently negative, less than 2 per cent died. The pneumococcus specific substance continues to be excreted in the urine during the patient's convalescence, and in explanation of this phenomenon it is suggested that the polysaccharide, as antigen, is gradually dissociated from the antibody and slowly excreted by the kidneys.

FROM AUTHOR'S SUMMARY.

Microbiology and Parasitology

BACTERIOLOGIC STUDIES OF AN EPIDEMIC OF PLEURODYNIA. M. L. COOPER and H. M. KELLER, Am. J. Dis. Child. **54**:231, 1937.

Blood, cerebrospinal fluid, nasopharyngeal material, nasal washings and Seitz filtrates of nasal washings, and stools from 26 children suffering from an epidemic of pleurodynia during the summer of 1935 were studied by means of cultures and by injecting them into monkeys, rabbits and Swiss mice. A slightly hemolytic green-producing streptococcus was found in the culture from the upper respiratory tract of every patient. However, this finding did not permit any etiologic conclusion, for the same bacterium was found consistently in the throat of every patient of the community during several years preceding the investigation. Blood cultures and spinal fluid cultures from the patients remained sterile. Some of the animals died following the inoculations. At necropsy these animals showed congestive and hemorrhagic lesions in the lungs and degenerative changes in the liver, spleen and kidneys.

I. DAVIDSOHN.

AN INFECTION OF CHICK EMBRYOS WITH HAEMOPHILUS PERTUSSIS REPRODUCING THE PULMONARY LESIONS OF WHOOPING COUGH. M. GALLAVAN and E. W. GOODPASTURE, Am. J. Path. **13**:927, 1937.

Chick embryos are susceptible to infection with Haemophilus pertussis. Infection of the respiratory tract, including the lungs of the embryo, has been induced by infection of the chorioallantoic membrane and by inoculation of the amniotic fluid with H. pertussis. The pulmonary lesions of human whooping cough are reproduced in detail by the pulmonary infection of the embryo. These are characterized by growth of H. pertussis on the ciliated border of respiratory (and other) ciliated epithelia, necrosis and inflammation of the middle and basal layers of the epithelial membrane, intrabronchial and peribronchial cellular exudation and alveolar and interstitial pneumonia. These experiments indicate that H. pertussis alone is the inciting cause of whooping cough. FROM AUTHORS' SUMMARY.

SPECIFICITY OF THE LESION OF EXPERIMENTAL MUMPS. O. BLOCH JR., Am. J. Path. **13**:939, 1937.

Focal acinar necrosis, i. e., necrosis involving all or most of the cells of an acinus, is the fundamental lesion of experimental mumps, the lymphocytic reaction, edema and hemorrhage being subsequent factors. None of the inert or infectious substances injected give this particular type of necrosis, though some of them

may cause the death of a cell here and there or produce an abscess destroying large numbers of acini. Cytoplasmic inclusion bodies, though found in over half the cases of mumps, may also be found in glands which have received an injection of normal saliva and cannot therefore be regarded as a specific sign of mumps infection. The abundance and interacinar location of the lymphocytic exudate are suggestive evidence that the lesion is due to infection rather than to an inert substance but do not aid in distinguishing between different types of infection. It should be stated that in no condition other than mumps did a secondary enlargement, with edema of the gland associated with elevation of temperature, occur. This seems to be characteristic of mumps, as is likewise the histologic lesion.

FROM AUTHOR'S CONCLUSION.

FAILURE OF ALLERGIC INFLAMMATION TO PROTECT RABBITS AGAINST INFECTION WITH VIRULENT PNEUMOCOCCI. P. R. CANNON and G. HARTLEY JR., Am. J. Path. **14**:87, 1938.

These experiments offer no support to the view that an inflammatory reaction can develop quickly enough to prevent the escape of virulent bacteria from their site of lodgment in previously noninflamed tissue and cast further doubt on the validity of the hypothesis that a mechanical "walling-off" is an important mechanism of bacterial fixation in a nonimmune animal.

FROM AUTHORS' CONCLUSION.

VISCERAL LESIONS IN HAITIAN TREPONEMATOSIS. C. V. WELLER, Am. J. Syph., Gonor. & Ven. Dis. **21**:357, 1937.

In view of the impossibility of establishing an indubitable clinical diagnosis for each patient, this study must not be considered as offering proof of either the unity or the duality of yaws and syphilis. It is intended only as an objective presentation of factual material. However, one of three conditions must exist: Yaws and syphilis are essentially the same disease; or the group of patients here considered has an extremely high incidence of syphilis, and the evidences of this disease alone are apparent in the viscera; or yaws and syphilis, though different diseases, produce identical visceral lesions.

AN EPIZOOTIC DISEASE OF FERRETS DUE TO A FILTRABLE VIRUS. C. A. SLANETZ and H. SMETANA, J. Exper. Med. **66**:653, 1937.

An epizootic disease of ferrets with a high fatality rate is described. By the use of suitable material the natural disease can be transmitted experimentally. The primary causative agent of the disease is a filtrable virus. Secondary invasion of the infected animal by bacteria of the respiratory tract frequently occurs. The most important secondary invader is the hemolytic streptococcus. There seems to be no immunologic relationship between the virus of the ferret disease and the virus of canine distemper or that of human influenza. Histologically the disease is characterized by inclusion bodies in the cytoplasm and nuclei of epithelial cells of many organs. These inclusion bodies are indistinguishable from those occurring in canine distemper.

FROM AUTHORS' SUMMARY.

SPOTTED FEVER. H. PINKERTON and G. M. HASS, J. Exper. Med. **66**:729, 1937.

Comparative studies were made of the micro-organisms present in dog ticks (Dermacentor variabilis). Some of the ticks served as a control series; the remainder were exposed to infection with Dermacentroxenus rickettsii and thereafter were maintained under various conditions. All the female ticks contained in their ovaries coccoid intracellular micro-organisms. About 50 per cent of the ticks after refeeding contained rickettsia-like micro-organisms in variable numbers in nearly all organs. The groups of ticks exposed to infection with the virus of spotted fever, in addition to the micro-organisms mentioned, usually harbored large

numbers of D. rickettsii, distinguishable with certainty from the nonpathogenic organisms only by their localization in the nuclei of tick cells. No influence on the size, number or distribution of either the nonpathogenic rickettsias or of D. rickettsii in ticks was attributable to refeeding, variations of the temperature of incubation or variations of the length of the period of incubation. Pinkerton and Hass conclude from the results of these studies that the nonpathogenic rickettsias which occur in these ticks have no well defined relationship to D. rickettsii, since they differ from the latter organism not only in the absence of virulence and immunizing properties but also in their distribution in tick tissues and in their inability to multiply in the nuclei of cells. FROM AUTHORS' SUMMARY.

THE VIRULENCE OF SMOOTH, ROUGH AND RESPIRATORY STRAINS OF HAEMOPHILUS INFLUENZAE. C. A. CHANDLER, L. D. FOTHERGILL and J. H. DINGLE, J. Exper. Med. **66**:789, 1937.

A comparative study of the virulence of smooth, converted rough and respiratory strains of Haemophilus influenzae was carried out by injection of mucin suspensions of the organisms into mice. The smooth strains were found to be significantly more virulent than either the converted rough or the respiratory strains. The converted rough and the respiratory strains were found to be approximately equal in virulence. A diminution in virulence was observed in smooth strains which had dissociated spontaneously, either partially or completely.

FROM AUTHORS' SUMMARY.

GENESIS AND REVERSION OF A BACTERIOPHAGE. A. I. KENDALL and C. A. COLWELL, J. Infect. Dis. **61**:303, 1937.

Attention is directed to the somewhat ambiguous use of the terms "lytic," "lysogenic" and "resistant" (neutral) in discussing bacteriophage. Some of the actual interrelations among lytic, lysogenic, resistant and neutral cultures are herein described and discussed. A series of neutral cultures was obtained from a strain of Bacterium coli (coli CH). Specific phages for each were developed from sewage. Each successive neutral culture was unaffected by the phage through which it was obtained. Phages for the first and fourth neutral cultures of this series lysed the ancestral (CH) culture. Phages for the second and third neutral cultures of this series did not lyse the ancestral culture. Phages prepared for these several neutral cultures did not anticipate; i. e., a phage lysing an earlier member of the culture series did not act on a later member of the culture series. Reversion of the phage of the fourth neutral culture on the parent (CH) culture resulted eventually in phage acting only on the ancestral (CH) culture. Neutral cultures obtained from reverted phage (N4–CH5 phage) and CH organism were lysed by four separate sewage phages made at different times for the CH (parent) organism. These four separate sewage phages were alike in essential details of potency and specificity. However, certain minor differences were detectable by the use of neutral cultures; that is to say, although these phages were apparently alike, a neutral culture resistant to one of these phages was not necessarily resistant to the others. From these observations it appears that minor differences are detectable among phages prepared for a specific culture under similar conditions, but with different samples of the same inciting agent. Also it seems from these observations that phages partake of the character of specific bacteria and do not act as independent, immutable entities.

FROM AUTHORS' SUMMARY.

THE CULTIVATION OF RABIES VIRUS IN TISSUE CULTURES. H. BERNKOPF and I. J. KLIGLER, Brit. J. Exper. Path. **18**:481, 1937.

Experiments are reported indicating that it is possible to cultivate fixed rabies virus in mediums containing embryonic rat or mouse brain. Serial subcultures

were obtained in a medium consisting of chicken plasma covered with Tyrode serum. Rabbit serum may be used for the latter, although human serum is better. The procedure reported by Webster and Clow is more satisfactory for mass cultures. In their medium no growth was obtained with rabbit serum, but successful serial passages were made in mediums containing either monkey or human serum. The virus cultures incubated at 30 or 37 C. increase in virulence up to about the sixth or seventh day. Thereafter the virulence declines and disappears by the twentieth day. Formaldehyde solution (1:1,000) inactivates the cultures if they are kept one hour at 37 C. and then for forty-eight hours at ice box temperature; the rate of inactivation appears to depend on the concentration of the formaldehyde.

FROM AUTHORS' SUMMARY.

INFLUENZA VIRUS INFECTION OF RATS AND GUINEA PIGS. C. H. STUART-HARRIS, Brit. J. Exper. Path. **18**:485, 1937.

Influenza virus that has been passed through ferrets will produce an inapparent infection in the rat and guinea pig. Virus is recoverable from both the nose and the lungs of the rat after inoculation under an anesthetic, but only from the nose of the guinea pig. In neither animal is the infection transmissible by contact.

FROM AUTHOR'S SUMMARY.

AUJESZKY'S DISEASE. P. REMLINGER and J. BAILLY, Ann. Inst. Pasteur **59**:5, 1937.

This "pseudorabies" has now been described in many countries of Europe and of the Americas. The reported difficulty in transmitting the virus to animals was attributed to the erratic distribution of the virus in infected animals. The authors were uniformly successful in various types of transfers. Bite wounds were considered rarely infectious, but evidence that dogs and cats might be infected by feeding on infected material suggested an autonomy for this virus. Immunization with this virus was also difficult. A curious phenomenon observed was that 71 per cent of the animals died at night, particularly dogs. Preserved in a glycerin suspension of cat brain at 6 C., the virus survived not less than four years. Strains of virus from different countries appeared to be the same, and the authors make a plea that biologists be spared the complexity of the A, B, C and D strains of the Aujeszky virus and of the para and pseudo terms.

M. S. MARSHALL.

CERTAIN STREPTOTHRICES. R. K. GOYAL, Ann. Inst. Pasteur **59**:94, 1937.

A thorough laboratory study of 11 strains of Streptothrix revealed that spores were no more resistant than filaments to heat; that sulfuric acid was not always reliable in isolation of the bacteria (for removal of contaminants), and that the p_H was not reliable for differentiation. The virulence for guinea pigs was slight, but superinfection yielded more intense lesions than primary infection. Experiments revealed an antigen common to the tubercle bacillus, the streptothrices and the diphtheria bacillus.

FROM AUTHOR'S SUMMARY.

THE YERSIN TYPE OF TUBERCULOUS TOXICOSIS-INFECTION OF THE RABBIT. F. VAN DEINSE, Ann. Inst. Pasteur **59**:182, 1937.

The Yersin type of tuberculosis is a toxicosis-infection in which the lesions are due partly to the virulence of the organism and partly to its toxicity. The toxic action increases when allergy appears and is enhanced by metabolic disturbances due to lesions of the organs. Cytologic examination of the blood confirms this toxic action.

FROM AUTHOR'S SUMMARY.

REACTIONS OF THE TISSUES IN EXPERIMENTAL MALARIA OF GOLDFINCHES (CARDUELIS CARDUELIS). V. MOLDAVSKA-KRITCHEVSKAVA, E. EINHORN and L. SOUKHOVA, Ann. Inst. Pasteur **59**:219, 1937.

During the incubation period (from the first to the seventh day), before plasmodia appear in the blood, swelling of the vascular endothelium and perivascular thickening are observed in all organs rich in reticuloendothelial elements, especially in the liver and spleen.

During the febrile period (from the seventh to the thirty-first day) numerous parasites appear in the peripheral blood, and hyperplasia and an excess of melanin are observed, first in the liver and spleen, then in all the organs. The reaction of the reticuloendothelium is extremely marked.

During the chronic "latent" phase (from the thirty-first to the sixtieth day) few or no organisms are found in the blood, and the hyperplasia and excess of melanin in the liver and spleen are decreased, although a large amount of pigment remains for a long time. The manifestations of reticuloendothelial reaction subside, and melanin gradually disappears from the organs.

FROM AUTHORS' SUMMARY.

CULTIVATION OF THE VIRUS OF FOOT AND MOUTH DISEASE IN PURE CULTURES OF EPITHELIAL CELLS AND FIBROBLASTS. K. KÖBE and H. FIRTIG, Zentralbl. f. Bakt. (Abt. 1) **138**:14, 1936.

The virus of foot and mouth disease grew well in pure cultures of epithelial cells from the iris of guinea pig embryos. Epithelial cells furnished a better nutrient medium than did the whole skin. The virus neither developed nor maintained itself in pure cultures of fibroblasts from the skin and subcutaneous tissues of guinea pig embryos. The practical difficulties of the method rest mainly in the cultivation of large enough numbers of epithelial cells, but the experiments demonstrate that the cultivation of the virus can be improved by adding to the culture medium a pure culture of epithelial cells.

PAUL R. CANNON.

CULTIVATION OF THE VIRUS OF PSITTACOSIS. E. HAAGEN and B. CRODEL, Zentralbl. f. Bakt. (Abt. 1) **138**:20, 1936.

Psittacosis virus from various sources was grown through many transfers in single drop tissue cultures and in fluid mediums according to the method of Maitland and Maitland. During this cultivation no changes in the biologic and pathogenic properties of the virus were observed. Survival and growth of the virus in the test tube depend on the presence of living cells. In the absence of such cells or after the mixture of dead tissue with the culture medium, the virus dies quickly. The development of the virus occurs intracellularly, in epithelial and endothelial cells. The article contains several photomicrographs showing psittacosis bodies within the cytoplasm of cells taken from the tissue cultures.

PAUL R. CANNON.

THE VIRULENCE OF VACCINE VIRUS IN TISSUE CULTURE. E. HAAGEN and B. CRODEL, Zentralbl. f. Bakt. (Abt. 1) **138**:27, 1936.

The authors tested out various methods for the culturing of vaccinia lymph in tissue culture, using the single drop method, the Maitland method and the chorioallantoic method of Goodpasture. They found all three methods successful, and after ten passages the virus, in a dilution of 1:50, gave strong reactions when injected into the testicles of rabbits.

PAUL R. CANNON.

Tumors

CHEMICAL COMPOUNDS AS CARCINOGENIC AGENTS. J. W. COOK and others, Am. J. Cancer **29**:219, 1937.

The various groups of carcinogenic chemical compounds are classified and discussed in the light of their chemical relationships and their biologic effects. The most active cancer-producing compounds yet encountered belong to the cholanthrene group and are of special interest on account of their relationship to the bile acids. The carcinogenic properties of 3,4-benzpyrene, a constituent of coal tar, have now been extensively investigated, and the broad principles of molecular structure necessary for activity within the group of hydrocarbons and allied heterocyclic compounds related to 1,2-benzanthracene have been laid down. Results of interest have been obtained with water-soluble carcinogenic agents, one of them being a substance related to 1,2-benzanthracene, and another being a styryl quinoline of quite different structure. Weak carcinogenic activity has also been found in a number of hydrocarbons not related to benzanthracene. Recent work of Japanese investigators has shown that pathologic effects, such as cholangioma, adenoma of the liver, hepatoma and carcinoma of the bladder, can be produced by feeding relatively simple azo compounds. Little progress has been made in elucidating the mechanism of the production of cancer by chemical compounds, but it is possible to enumerate a number of genetic and other factors which influence carcinogenesis. Many different mediums have been used for the administration of carcinogenic compounds, and control experiments with the mediums are important. Tumors have been produced by as little as 0.4 microgram of 1,2,5,6-dibenzanthracene, and instances of the early appearance of tumors following the application of carcinogenic compounds are recorded. In a table the authors summarize the production of cancer by five compounds in a variety of tissues and species. They discuss in some detail the role of estrogen in the production of tumors, describe the various systemic effects of carcinogenic compounds and refer to the problem of pulmonary tumors encountered in experimental work on carcinogenesis, to experiments on the transmission of chemically produced tumors by cell-free materials and to tissue culture. FROM AUTHORS' SUMMARY.

PRIMARY CARCINOMA OF THE LUNG. L. F. FRISSELL and L. C. KNOX, Am. J. Cancer **30**:219, 1937.

This article reports the results of a detailed analysis of the clinical and pathologic observations in forty-six cases of carcinoma of the lung. The pathologic features are summarized as follows:

Pulmonary tumors are essentially bronchiogenic, and their morphology varies according to the type and degree of differentiation assumed by the lining cells of the bronchi or bronchioles. Grossly they may be classified as hilar, nodular parenchymatous, peripheral, diffuse or bilateral miliary lesions. Microscopically Frissell and Knox have classified them as squamous carcinoma, adenocarcinoma and undifferentiated carcinoma, the latter including small round cell, oat cell or spindle cell, medullary and basal cell types. Metastasis ultimately takes place with each of these types, practically 100 per cent to the peribronchial nodes. Widespread metastases are the rule with adenocarcinoma, and massive mediastinal metastases with the medullary and small cell types.

PAPILLARY CARCINOMA (MALIGNANT PAPILLOMA) OF THE CHOROID PLEXUS. O. A. TURNER and M. A. SIMON, Am. J. Cancer **30**:289, 1937.

The literature on papilloma of the choroid plexus is reviewed, and two cases of papillary carcinoma of the choroid plexus of the third ventricle are reported. Of the seventy-two recorded cases of papilloma of the choroid plexus, only a few (seven ?) have been considered as instances of carcinoma.

ETIOLOGY OF CANCER OF THE MAMMA IN MICE AND IN MAN. W. CRAMER, Am. J. Cancer **30**:318, 1937.

The experimental production of cancer of the mamma by means of estrogenic substances has enlarged the outlook on the problem of the etiology of cancer by demonstrating a carcinogenic environment which is entirely internal. In that respect there is an essential difference from experimental carcinogenesis of the skin, in which the decisive factor is a carcinogenic agent acting from without and in which the carcinogenic environment is partly external and partly internal. The existence of a carcinogenic environment which is entirely internal enables one to understand why malignant growth can develop in organs not exposed to influneces coming from without; why it is possible to obtain by inbreeding pure strains of mice with a high incidence of spontaneous cancer in one organ (the mamma) but not in another (the skin), and why such pure strains show considerable differences from each other and from mixed strains in the response of the mamma to the carcinogenic action of estrogenic substances, while in the same strains no such differences are found in the response of the skin to chemical substances carcinogenic for the skin. In man the familial incidence of cancer shows corresponding differences between the mamma, where the familial incidence is high, and the lip, where it is low. The inference is that cancer of the breast in women—at least in those with a family history of cancer of the breast—is the result of an internal carcinogenic environment. Since in mice this internal carcinogenic environment is associated with abnormalities in the endocrine system, a search for such abnormalities in women with cancer of the breast and a family history of such cancer is indicated.

FROM AUTHOR'S SUMMARY.

PRODUCTION OF SPONTANEOUS MELANOTIC NEOPLASMS IN FISHES BY SELECTIVE MATINGS. M. GORDON, Am. J. Cancer **30**:362, 1937.

Spontaneous melanotic neoplasms may be produced in fish by selecting their parents properly. To do this it is necessary to select as one of the parents a platyfish (Platypoecilus maculatus) which carries the large black pigment cells, here called macromelanophores, and mate it to a swordtail (Xiphophorus herlleri). When the cross is made as stated, melanosis develops in the hybrid fish that inherit macromelanophores. The platyfish may have micromelanophores as well as macromelanophores. The platyfish that is stippled as well as spotted, when used as a parent with the swordtail, has hybrid offspring in which melanosis occurs. But the platyfish with micromelanophores only or with no melanophores fails to bring melanosis to the hybrid offspring of its mating with the swordtail. A swordtail parent may have micromelanophores or no melanophores, but it produces melanotic hybrids if mated to a spotted (macromelanophore) platyfish. Hybrid fishes have been observed with one type of melanophores only—macromelanophores. The presence of both micromelanophores and macromelanophores may intensify the melanotic tumor in the hybrid fish, but the presence of micromelanophores is not essential to the melanotic state. The presence, as demonstrated by genetic methods of breeding, of but one type of melanophore in a neoplastic melanotic tumor clarifies the histologic interpretation of the cellular elements involved.

Melanotic neoplasms have been observed in seventy hybrid fishes on the day of their birth. These melanotic day old fishes have been produced in two ways: (*a*) by inbreeding the first generation hybrids, one of which was melanotic; (*b*) by crossing a heavily melanotic first generation hybrid fish back to the swordtail parent. Previous work has shown that if a melanotic hybrid is crossed back to the platyfish parent instead of to the swordtail the state of melanosis in the offspring approaches the normal condition. Melanotic tumors have been observed in day old fish with micromelanophores as well as macromelanophores. But some day old fish had tumors consisting of macromelanophores alone.

FROM THE AUTHOR'S SUMMARY.

CANCER AND HUMAN RACES. C. BONNE, Am. J. Cancer **30**:435, 1937.

About cancer in truly primitive tribes nothing is known. If such tribes are within reach of medical supervision, the first tumors that come under observation are those on the surface of the body, such as cancer of the skin or of the penis, or those causing foul discharges and disturbances of elemental bodily functions, such as cancer of the jaw or of the uterus. Before there can be an opinion on the frequency of the various forms of internal disease, including cancer, there must be hospitals with regular autopsy services, but the figures from such hospitals must be interpreted with caution. The figures are useful, however, particularly as they indicate peculiarities as to the sites of incidence of cancer throughout the body. There is a remarkably high frequency of primary carcinoma of the liver in cirrhotic livers, independent of helminthic infections, in various parts of the tropics, especially in the Far East. There is a nearly total absence of gastric cancer among the native Malay population of Java, associated with a similar scarcity of gastric ulcer, though the Chinese in Java and in the tropical parts of the Far East generally have the usual amount of gastric carcinoma and gastric ulcer. There is a peculiar frequency of primary malignant tumors of cervical lymph nodes with reticulo-endothelial origin in Java, Sumatra, Singapore, the Philippine Islands, Indo-China and other parts of the Far East. Cancer of the skin of the legs is of frequent occurrence among male Malays, developing on old neglected ulcers of various nature. Whether these peculiarities are due to inborn racial influences or to the special conditions of life of the Far East remains to be studied. Figures are available for the total mortality from cancer in certain parts of Sumatra, where the Chinese and Malay population of the tobacco and rubber estates is registered and hospital service and medical attendance are of a high standard. When the cancer rate here is recalculated for a population of standard age, the total mortality is in accord with the usual figures for Western countries.

FROM AUTHOR'S SUMMARY.

MALIGNANT RHABDOMYOBLASTOMA OF THE SKELETAL MUSCULATURE. A. I. RAKOV, Am. J. Cancer **30**:455, 1937.

Careful histologic study of malignant tumors arising in skeletal muscles reveals that a considerable percentage of these tumors are rhabdomyoblastoma. Rhabdomyoblastoma is characterized by : (*a*) polymorphism of the cells of which it is composed; (*b*) presence of spindle shape cells and of syncytia; (*c*) presence of giant cells; (*d*) a characteristic pattern of the stroma; (*e*) presence of myofibrils in the tumor cells. Two types of rhabdomyoblastoma can be distinguished: the mature and the immature. Rhabdomyoblastoma may develop in persons of any age. The course is sometimes protracted. Radiation is of no benefit, and surgical intervention is often followed by local recurrence, with eventual metastasis.

FROM AUTHOR'S SUMMARY.

RECOVERY IN LOCKE'S SOLUTION OF A RETARDING AGENT FROM IMMUNE RATS. W. H. WOGLOM, Am. J. Cancer **30**:477, 1937.

A method is described for extracting from rats resistant to sarcoma 39, and recovering in Locke's solution, the agent which causes this growth to regress. Evidence is adduced to show that at least some of this agent can be adsorbed on charcoal.

FROM AUTHOR'S SUMMARY.

METASTASES IN SQUAMOUS CELL CARCINOMA. E. M. BURKE, Am. J. Cancer **30**:493, 1937.

Metastatic lesions were found in 37 per cent of a series of 186 patients with carcinoma arising in squamous epithelium, a greater frequency than is usually reported. Males are more apt to have malignant lesions in squamous epithelium than females. Only a small number of these patients gave a history of carcinoma

in the family or had a positive Wassermann reaction. Such factors as the duration of the disease and the site of the primary lesion seemed to have little or no bearing on the production of distant metastases. Histologic grading of the primary tumor showed that in the majority of cases in which distant metastases occurred the primary growth was in the more malignant group. Primary squamous cell carcinoma in some locations is more prolific in the formation of distant metastases than it is in other locations. The lungs and liver are as a rule the major recipients of metastatic implants; the adrenals and bone receive them in a lesser degree.

FROM AUTHOR'S SUMMARY.

NUCLEAR ABNORMALITIES RESULTING FROM INHIBITION OF MITOSIS BY COLCHICINE AND OTHER SUBSTANCES. A. M. BRUES and E. B. JACKSON, Am. J. Cancer **30**:504, 1937.

Single injections of colchicine have been given to rats following partial hepatectomy. This treatment causes an arrest of normal cell division at about the beginning of the metaphase. Large numbers of abnormal figures therefore occur in the rapidly dividing hepatic cells of these animals. They appear at first in clear, rounded, readily ruptured cells, in which the spindle cannot be seen and in which the chromosomes are widely scattered. Between twelve and forty-eight hours after the drug is given, large numbers of cells with bizarre nuclear figures appear, notably cells with numerous miniature nuclei and cells with single large nuclei of ameboid shape. It is suggested that these figures represent a specialized mode of recovery from arrested mitosis, in which individual chromosomes or small groups of chromosomes swell to form one or more resting nuclei. In the case of sarcoma 180, complete arrest of mitosis at an early stage of the metaphase is not seen, in contrast to what occurs in the liver. In all preparations studied, a few cells can be seen in later stages of division. In some grafted tumors the toxic effect of colchicine on mitosis is evident only around the margin of the tumor.

FROM AUTHORS' SUMMARY.

SKIN IRRITATION AND CANCER IN THE UNITED STATES NAVY. S. PELLER and C. C. S. STEPHENSON, Am. J. M. Sc. **194**:326, 1937.

The peculiar conditions of life in the United States Navy—the prolonged exposure to the sun's rays, to open air and to salt water—are associated with (*a*) a frequency of cancer of the skin and of the lip eight times normal and (*b*) a greatly diminished morbidity and mortality from all other cancers. About four tenths of the men who would be expected to die from an inner cancerous growth presented instead a curable tumor of the skin or of the lip. The mortality from cancer of the skin and of the lip in the United States Navy is about three times higher than that in the average population (of the same composition as regards age). Among the fatal cancers melanoma predominates. The danger from epithelioma is small. It seems that only a small part of the patients who have been cured of cancer of the skin or of the lip produce later cancer of an inner organ. This problem must be studied on a larger scale. By exposing young men to strong cutaneous irritants which are not carcinogenous to inner organs, the lives of some who would die from internal cancer might be saved, at least for a certain number of years.

FROM AUTHORS' SUMMARY.

PNEUMONOCONIOSIS AND PULMONARY CARCINOMA. A. J. VORWALD and J. W. KARR, Am. J. Path. **14**:49, 1938.

If inhaled dust is of etiologic significance in the development of primary pulmonary carcinoma, the following two conditions should obtain: 1. The incidence of pulmonary tumor in pneumonoconiotic persons should be higher than in the general population. 2. The dust in question should be irritating to the pulmonary parenchyma and capable of producing proliferation and carcinomatous transformation of epithelial tissue. Vorwald and Karr state that a compilation of their

observations in roentgenologic, postmortem and experimental studies shows that these conditions do not obtain. A compilation of roentgenologic observations from the literature on the lungs of 57,362 males exposed to occupational dusts revealed only 3 patients with primary pulmonary carcinoma, or an incidence of 0.005 per cent. The Saranac laboratory surveys, which comprise stereoscopic roentgenograms of the chests of 15,587 males exposed to dust, showed an incidence of 0.019 per cent. Postmortem examination of 3,738 animals exposed to many different kinds of dust for long periods disclosed 2 guinea pigs with pulmonary neoplasm. In both the tumors were similar and were interpreted as benign adenoma. All other animals failed to show irritation, hyperplasia or tumorous transformation of the epithelium lining the respiratory passages. This was observed irrespective of the activity of the dust, i. e., whether it was inert or had caused marked fibrosis of the pulmonary connective tissue. Inhaled dusts, therefore, except those containing recognized carcinogenic substances, such as radium and tar, cannot in general be considered as etiologic factors in the development of primary pulmonary carcinoma.

FROM AUTHORS' SUMMARY.

EFFECT OF ROENTGENOTHERAPY ON GLIOMA. I. M. TARLOV, Arch. Neurol. & Psychiat. **38**:513, 1937.

According to Tarlov, with roentgen therapy glioma generally undergoes histologic changes. Especially are changes evident in medulloblastoma, which shows decrease of tumor cells and their replacement by connective tissue. Increase of connective or fibrillary glia tissue also occurs to some extent in other types of glioma (glioblastoma multiforme, astroblastoma, astrocytoma) and is associated with some regressive histologic changes, such as cystic degeneration and increase of necrosis. Such changes, however, are inconstant and often could not be attributed to treatment. Tarlov emphasizes "the possibility of damage to blood vessels (with hemorrhage and softening) and to nerve cells of the brain" when large doses of roentgen rays are administered.

GEORGE B. HASSIN.

PRODUCTION OF OSTEOSARCOMA IN A MOUSE BY THE INTRAMEDULLARY INJECTION OF 1,2-BENZPYRENE. A. BRUNSCHWIG and A. D. BISSELL, Arch. Surg. **36**:53, 1938.

An osteosarcoma (bone-forming sarcoma) developed in the tibia of a mouse which had received an intramedullary implantation of a mixture of 1,2-benzpyrene and cholesterol eight and one-half months previously. It appears that this is the first instance recorded of experimental production of osteosarcoma by a chemical agent. Previously osteosarcoma and fibrosarcoma of bone have been produced experimentally only by irradiation. Thus osseous tissue may be added to the list of tissues in which malignant degeneration has been produced by means of 1,2,5,6-dibenzanthracene, 1,2-benzpyrene and methylcholanthrene. In one of another series of rats in which pellets of methylcholanthrene and cholesterol had been injected into the lower ends of the left femurs, fibrosarcoma of bone developed after twelve months.

FROM AUTHORS' SUMMARY.

SPONTANEOUS MAMMARY TUMORS IN MICE. L. L. ASHBURN, Pub. Health Rep. **52**:915, 1937.

This report represents the data from 480 female mice with spontaneous mammary carcinoma. The mice belong to strain 3 developed at the State Institute for the Study of Malignant Disease, Buffalo. Metastases occurred in 217 (45.2 per cent) of these mice. Multiple tumors occurred in 61.5 per cent with an average of 2.08 tumors per mouse. The incidence of metastasis is higher in mice having multiple tumors and in those with tumors of long duration than in those with single or small tumors. Tumor size per se has little effect on the incidence of metastasis; this is especially true with reference to tumors of long duration. Rapidly growing tumors metastasize early and frequently. Tumors showing diffuse

undifferentiated cellular areas metastasize more frequently than those of relatively pure glandular structure. In subdividing the mammary carcinomas, little if any difference in clinical malignancy was seen between the histologic groups usually used. Location of the primary growth has little if any effect on the tendency to metastatize. Nonpulmonary metastases are infrequent; the location and number are given. Tumors other than those of mammary origin are relatively infrequent. Those found were adenoma of the lung and tumors of the lymphatic apparatus.

FROM AUTHOR'S SUMMARY.

OXYGEN POISONING AND TUMOR GROWTH. J. A. CAMPBELL, Brit. J. Exper. Path. **18**:191, 1937.

De Almeida's destruction of Rollo's tumor in the living rat with high oxygen pressure could not be confirmed with the different tumors (rat and mouse) used in the present work. His finding that starved rats tolerate higher oxygen pressure than do fed rats is confirmed. It is shown for the first time that external temperature may exert an effect on oxygen poisoning. Exposing white rats to 6 atmospheres of oxygen for thirty minutes at 33 C. usually results in death. The fall (by 10 C.) of body temperature observed in oxygen poisoning is thus protective.

FROM AUTHOR'S SUMMARY.

EFFECTS OF ROAD DUST FREED FROM TAR PRODUCTS ON THE INCIDENCE OF PRIMARY PULMONARY TUMORS IN MICE. J. A. CAMPBELL, Brit. J. Exper. Path. **18**:215, 1937.

It was shown previously that dust from tarred roads causes cancer of the skin of mice. Road dust minus tar, removed by benzene, does not cause cancer of the skin of mice; it stimulates the production of pulmonary tumors in mice but not to so great an extent as when the tar is also present. Pulmonary tumors are rare in mice before they are 12 months of age. The dust does not cause any obvious inflammatory reaction—apart from the tumors themselves—in the lungs or lymph glands. Perhaps the presence of pulmonary tumors among some of the control mice is due in part to the dust breathed from the contents of their boxes or from the general atmosphere. This dust may contain a carcinogenic agent, e. g., tar, or it may "irritate" the lung without obvious inflammatory reaction. Tar, either by direct action on the lung itself or indirectly by some action on other tissues or both, stimulates the production of pulmonary tumors in mice and hastens their appearance. Metastases from such tumors in mice are recorded by Campbell, for the first time in Great Britain so far as he knows. The majority of these tumors in the dusted mice are malignant.

FROM AUTHOR'S SUMMARY.

LYMPHOSARCOMA. E. K. DAWSON, J. R. M. INNES and W. F. HARVEY, Edinburgh M. J. **44**:645, 1937.

Lymphosarcoma, or reticulum sarcoma, is defined as a radiosensitive tumor of lymphoid tissue, arising from the embryonal stem cells of that tissue. The authors hold that the "lymphosarcoma of smaller or larger cell type arises from an undifferentiated or little differentiated mesenchymal cell which constitutes in adult life the stem-cell of lymphoid tissue and has, *in situ*, the productive potentialities of reticuloblast, fibroblast and lymphoblast."

EFFECT OF ROENTGEN RADIATION ON THE PRODUCTION OF SARCOMA BY A CHEMICAL COMPOUND IN MICE. W. V. MAYNEORD and L. D. PARSONS, J. Path. & Bact. **45**:35, 1937.

Irradiation of mice either previous to or during their reception of injections of sodium 1,2,5,6-dibenzanthracene-9,10-endo-$\alpha\beta$ succinate both accelerates the formation of, and gives rise to a greater number of, tumors. Irradiated mice

show a constant change in the blood immediately following irradiation. Irradiated and nonirradiated mice in which sarcoma is developing show a constant change in the blood at the time of appearance of the tumors. Eosinophil counts show a high peak at a variable point during the latent period in mice in which sarcoma is developing but this does not occur in mice which do not bear sarcomatous growths. A progressive rise in immature cells takes place in the blood of tumor-bearing mice, being greatest at the time of death. Control mice given injections of the compound and not acquiring tumors, as also controls given injections of physiologic solution of sodium chloride, whether irradiated or not, do not show immature cells in their blood except occasionally in small numbers such as are frequently found in the normal mouse.

FROM AUTHORS' SUMMARY.

SO-CALLED MUCINOUS CARCINOMA OF THE BREAST. K. HERZOG, Beitr. z. path. Anat. u. z. allg. Path. **99**:163, 1937.

Examination of thionine-stained and mucicarmine-stained sections of 9 specimens of so-called mucinous carcinoma of the breast, 8 of which were benign and characterized by local extension without metastases, revealed that the mucin is the product of the epithelial cells and not of the connective tissue cells. Its earliest appearance was observed in the form of dust and droplets in the cytoplasm of polygonal tumor cells. The mucin flowed out from the tumor cells into the stroma through artificially formed spaces and canals. On the other hand, the cells situated peripherally in the cords discharged their contents of mucin directly into the stroma. The evolution of the structure and character of the benign type was traced from the initial stage, characterized by solid cords of neoplastic epithelial cells, to the final dissolution. The author urges that the term carcinoma should not be used for mucin carcinoma of the benign type. In spite of the high frequency with which chronic mastopathia was associated with mucinous carcinoma in the 9 cases studied, no certain conclusion could be drawn as to a genetic relation between the two conditions.

R. J. LEBOWICH.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

ESMOND R. LONG, *Presiding*

Regular Meeting, Jan. 13, 1938

HERBERT L. RATCLIFFE, *Secretary*

TRENDS IN STATISTICS ON THE CAUSES OF DEATH IN PHILADELPHIA: A BRIEF ANALYSIS FOR THE CENTURY 1836-1936. ESMOND R. LONG.

An analysis of trends in statistics as to the causes of death must separate true causes from many that are fictitious. Nomenclature changes with the advance of medical science, and improvement in diagnosis steadily subdivides the larger categories of sickness into smaller ones. Out of the class of "fevers," for example, scientific progress split brain fever, meningitis and finally epidemic cerebrospinal meningitis. The recent recording of the bacteriologically distinct pneumonias, once all of them indistinguishable components of "lung fever," is another illustration of a trend in reported mortality based purely on refinement in diagnosis and nomenclature.

Obviously diseases, however common they are, cannot be recorded before they are discovered. Perforative appendicitis could not be mentioned in death records until it was recognized and placed in general medical consciousness in 1886. Prior to that, deaths caused by appendicitis appeared in the mortality columns in Philadelphia and elsewhere as deaths from peritonitis or inflammation of the bowels. Diseases calling for a special technic of recognition, as agranulocytosis, were forced to wait still longer.

The emphasis of the moment gives undue weight to a particular disease as a cause of death. A number of acute infections of the respiratory tract are characterized by symptoms almost identical with those of influenza, which can be diagnosed with certainty only by modern methods that are beyond practical general application. But the epidemic of 1918 made physicians "influenza conscious," and as a result much pneumonia that is not influenza in the strict sense and would not have been recorded as such before 1918 is now so reported.

In addition, and without more than mention of indifference in reporting causes of death and even occasional deliberate misrepresentation, there are many difficulties in assigning an exact cause of death, no matter how conscientious the reporter may be. The average length of life is increasing. A growing number of persons live to die of a combination of influences from the accumulating impairments of more years. Gradual deterioration of the heart is the result of such a combination, and some form of heart disease is usually selected by the physician for mention in the mortality report if some disability of this organ is finally apparent. A youth hypersensitive to certain foods may grow up to be a man with asthma in whom pulmonary emphysema develops, as a consequence of which the heart begins to fail, and finally pulmonary edema and hypostatic pneumonia are superimposed on "decompensation of the heart." The common final report of "myocarditis, with pneumonia a contributing cause," gives no inkling of the basic disease, nor does it separate the outcome in any way from heart failure and terminal pneumonia of entirely different origin.

These illustrations are cited because it is necessary to recognize the great limitations of any analysis from mortality returns. If the difficulties are clearly recognized, however, such an analysis has value. The study recorded here is based on the mortality statistics officially recorded for Philadelphia in 1861, 1886, 1911 and 1936, supplemented by the records of the Pennsylvania Hospital for

those years and 1836. During the seventy-five years between 1861, when vital statistics were first recorded, and 1936, the latest year of compiled returns, the recorded death rate fell from 25.6 to 12.3 per thousand. The greatest change in mortality in Philadelphia during those years was the change from a preponderance of deaths from the infectious diseases of early life to a preponderance of deaths from the so-called degenerative diseases of the late years of life. In this respect Philadelphia shares in a nation-wide trend. The six leading listed causes of death in Philadelphia are the same as those for the country at large.

In 1861 five diseases, tuberculosis of the lungs, typhoid fever, diphtheria (and croup), scarlet fever and smallpox, as reported, accounted for 34.7 per cent of the mortality in Philadelphia. In 1886 smallpox was all but extinct, but the remaining four still were credited with 34.9 per cent of the total number of deaths. In 1911 scarlet fever had almost joined smallpox as a negligible contributor to the death list, and diphtheria and typhoid fever were fast disappearing. In 1936 there were no deaths from smallpox, and typhoid fever, diphtheria and scarlet fever together made up only 0.13 per cent of the total mortality. Vaccination against smallpox, quarantine, the use of diphtheria antitoxin first and specific immunization later and progressive improvement of the water supply, as elsewhere, were largely responsible for the decrease in mortality from these five diseases. As a cause of mortality, pulmonary tuberculosis dropped from a high reported level of 14.1 per cent of the deaths in 1886 and a mortality rate of 283 per hundred thousand of population to 4.8 per cent of the deaths and a mortality rate of 60 per hundred thousand in 1936. The drop was indeed greater, for in the late years of the period from 1886 to 1936 the influx of a large number of Negroes, with a high death rate from tuberculosis, prevented the mortality rate, previously almost synonymous with the white mortality rate, from dropping as rapidly as it would have otherwise.

During the period covered the average age of the population increased about five years. The proportion of the population reaching the years over 70 was not greatly changed, but there was considerable increase in the percentage living to the sixth and seventh decades. Although deaths recorded as from "senility" or "old age" decreased as standards of reporting became more rigid (from 2.9 per cent of the total mortality in 1861 to 0.09 per cent in 1936), deaths from the various specific diseases of late life all increased. For example, the rate for deaths from diabetes rose steadily from a reported rate of 24 per hundred thousand of population (0.09 per cent of all deaths) in 1861 to 297 (2.4 per cent of all deaths) in 1936, and the rate for deaths from diseases of the prostate, chiefly enlargement, from 10 per hundred thousand (0.05 per cent of all deaths) to 68 per hundred thousand (0.5 per cent of all deaths) in 1936. Admittedly all of the increase cannot be accredited to the increase in the average age, as diagnosis improved in the interim. The recorded rate of deaths from cancer rose from an absurdly low level in 1861 to one probably corresponding far more closely to fact in 1936. Contributing to this increase were two known factors, better diagnosis and increase in the average age, and, as elsewhere in the country, perhaps several unknown factors as well. Four groups of malignant tumors, those of the breast, those of the digestive tract, those of the uterus and those of the respiratory system, accounted for 9 per cent of all deaths as reported in 1936 and for only 0.8 per cent of all deaths as reported in 1861. It is difficult to determine how the deaths from cancer that surely occurred in 1861 were reported, but many must have fallen into the columns of "senility," "dropsy," "inflammation" of various organs, "debility" and "marasmus."

As is well known, the largest number of deaths reported due to any one cause in late years has been that of deaths recorded as due to various defects of the heart and arteries. Of these, in turn, the major proportion are designated as from "myocarditis" or "myocardial degeneration," terms of little more significance than the obsolete term "senility." Indeed a large number of deaths are recorded simply as from "heart disease"—apparently a term still acceptable to compilers of vital statistics and to health departments, although "brain disease," once almost as

common in the mortality columns, is now obsolete. In brief, the vast number of deaths in the late years of life, due in large measure to cumulative illness, and previously reported vaguely under now outmoded or inacceptable terms, are at present reported equally vaguely under the mask of some ostensibly specified form of heart disease.

Of the six leading "causes of death" in 1936 only one, pulmonary tuberculosis, the sixth on the list, is a true disease entity. Cerebral hemorrhage, certainly a cause of death, the first on the list, might also be considered as an entity but not as a specific disease. "Diseases of the heart," "cancer and other tumors," "nephritis and other diseases of the kidney," respectively first, second and third on the list, even if correctly reported to the vague extent indicated by these terms, are obviously agglomerations of many diseases. "Pneumonia," fourth, represents a variety of anatomic types of acute respiratory disease of different bacterial or viral etiology.

It is impossible from examination of death returns to separate these agglomerations into their component parts, but there is no reason to doubt that in 1936 a far smaller proportion of residents of Philadelphia than in the years from 1836 to 1911, died of infectious and parasitic disease, and a much larger percentage from the numerous etiologically distinct diseases of the vascular system and different forms of malignant growth. Were it possible, however, to make such a separation, there is reason to believe that pulmonary tuberculosis, in spite of its great drop from the high level of former years, would be found still the chief cause of death in Philadelphia in terms of specific disease entities.

Table 1 summarizes trends in mortality returns as respects the infectious diseases of early life, on the one hand, and the diseases of late years, including cancer and diseases of the heart, on the other. Table 2, based on mortality returns for diseases of the brain, is added to illustrate the change in nomenclature and manner of reporting in the last three quarters of a century.

TABLE 1.—*Deaths from Various Causes Reported in Philadelphia, 1861-1936*

	1861		1886		1911		1936	
Population	565,000		971,000		1,580,000		2,028,000	
Approximate average age*	26 yr. (1860)		27 yr. (1890)		29 yr. (1910)		31 yr. (1930)	
Mortality per thousand	25.6		20.6		16.5		12.3	
	a†	*b*§	*a*	*b*	*a*	*b*	*a*	*b*
Infectious and parasitic diseases								
Tuberculosis of the lungs	3,634	12.6	2,834	14.1	1,973	11.3	597	4.8
Typhoid fever	580	2.1	618	3.1	149	0.9	8	0.06
Diphtheria and croup	1,612	5.9	1,061	5.3	325	1.9	5	0.04
Scarlet fever	2,380	8.6	2,480	12.4	119	0.7	4	0.03
Smallpox	1,516	5.5	4	0.02	1	0.004	0	0.0
Cholera	36	...	36	...	2	...	0	...
Typhus fever	90	...	6	...	0	...	0	...
Totals		34.7		34.9		14.8		4.9
Certain diseases chiefly of old age								
"Senility"	406	2.9	753	3.8	160	0.6	22	0.09
Diabetes	24	0.09	42	0.21	176	1.0	297	2.4
Diseases of the prostate	..	...	10	0.05	40	0.2	68	0.5
Myocardial disease, chronic disease of valves and coronary arteries	668	2.4	1,032	5.2	1,818	7.0	2,755	11.0
Cancer and other tumors								
Breast	18	0.06	54	0.3	86	0.5	150	1.2
Digestive tract	134	0.5	236	1.2	451	2.6	710	5.7
Uterus	60	0.2	124	0.6	145	0.8	153	1.2
Respiratory system	4	0.01	8	0.04	...	...	111	0.9
Totals		0.77		2.1		3.9		9.0

* This is calculated from the census return of the year indicated in parentheses.
† Column *a* records the approximation per million living.
§ Column *b* records the percentage in relation to the total number of deaths.

TABLE 2.—*Deaths from Disease of the Brain as Reported in Philadelphia in 1861 and 1936*

1861		1936	
Apoplexy	162	Cerebral hemorrhage	1,242
Palsy	159	Cerebral embolism and thrombosis	346
Congestion of the brain	275	Hemiplegia, cause unspecified	13
Dropsy of the brain	222	Dementia paralytica	82
Effusion on the brain	73	Encephalitis (epidemic and nonepidemic)	45
Softening of the brain	28	Meningitis (epidemic and nonepidemic)	90
Inflammation of the brain	305		
Disease of the brain	112		
Brain fever	7		

STREPTOTHRIX INFECTION OF THE INTESTINES ASSOCIATED WITH ACUTE APPENDICITIS. J. ALBRIGHT JONES and JOHN EGOVILLE.

A Negro girl of 2 years was admitted to the Philadelphia Hospital on the evening of March 16, 1937. At 8 a. m. the following morning, before examination was completed, she died. So far as could be determined, the first signs of illness were noted three days before admission to the hospital. Beginning at that time, she experienced a severe attack of intermittent abdominal pain and vomiting. This attack lasted for some twelve hours, after which she was free from pain and seemed fairly well for about twenty-four hours. A second attack of pain and vomiting developed approximately twenty-four hours before death and continued to the end.

Necropsy, eighteen hours after death, revealed the following changes in the abdomen: In the right lower quadrant a firm mass about the size of an orange was encountered. This consisted of an elongated S-shaped appendix, 11 by 1 cm., surrounded by a loop of ileum and the cecum. These were bound together by fine fibrous adhesions. The duodenum and jejunum were filled with a thin yellow watery material. Scattered through the submucosa of the terminal ileum were small firm nodules from 1 to 3 mm. in diameter. These were most numerous in the region adjacent to the ileocecal valve. Peyer's patches were oval, elevated and button shaped, with rolled edges, and had irregular superficial ulcerations covered with a hemorrhagic purulent material. The entire colon, including the appendix, also contained submucosal nodules, but so numerous were the nodules in the region of the cecum and ascending colon that that portion of the large bowel resembled a cobblestone pavement. Many of these nodules showed pinpoint abscesses; others were umbilicated. Lymph nodes at the ileocecal junction measured 3 by 2 cm. and were arranged in grapelike clusters. On section they were soft and beefy red. The remaining organs were free from these lesions. Cultures of the intestinal contents were negative for the typhoid group of organisms.

Microscopic examination of Peyer's patches and of the appendix and colon showed similar lesions. In the submucosa were large, irregularly oval masses of filaments that were believed to be Streptothrix. These were surrounded by a margin of round cells and epithelioid cells, supported by a loose fibrous stroma. Frequently, the lesions showed abscess formation with ulceration of the superficial mucosa and fungation into the lumen of the intestine. The lympahtic spaces of the submucosa frequently contained these filaments. The muscularis mucosae was normal. In the appendix alone did the inflammatory process extend to the serosa, and here the changes were those of acute suppurative appendicitis. In the lymph nodes the lesions were smaller; the collar of cells about the central filaments was frequently epithelioid, and abscesses were scarce.

THROMBOSIS OF THE PULMONARY ARTERY IN ANTHRACOSILICOSIS AND PULMONARY TUBERCULOSIS. ROBERT CHARR.

During 1937 24 patients with anthracosilicosis and 36 with pulmonary tuberculosis came to necropsy at the White Haven Sanatorium, in Pennsylvania; 7 of the group with anthracosilicosis and 2 of the group with pulmonary tuberculosis each presented thrombosis of one of the main branches of the pulmonary artery.

In 8 of these 9 patients the occlusion involved the right branch of the pulmonary artery, and in the ninth, the left. In every case the occluding clot varied from pink to white and was firmly adherent to the intima of the vessel at the posterior aspect. One could not remove these clots without breaking them.

The manner in which the platelets, fibrin and cellular elements of the blood were arranged on the walls of the atheromatous arteries suggested that the thrombi had been formed within the lumens of the vessels. The invasion of the coagula by strands of fibrous tissue originating from the thickened intima was another point in favor of primary thrombosis. In addition, the fact that each occlusion was limited to an artery whose terminal branches were located near cavities or within the masses of anthracosilicotic consolidation indicated that it was the result of the pathologic changes of the pulmonary tissues surrounding these branches and not the result of accidental lodgment of an embolus from some distant part of the body. It appears that the thrombosis of an artery began in the terminal points and was due to irritation of those points by tuberculosis or anthracosilicosis. Once thrombosis set in the process extended centrally, ultimately occluding the main branch to such an extent as to give rise to symptoms. In all of the cases the involved vessel was in a lung in which pulmonary disease was most extensive and vascular changes most marked. This is demonstrated by the postmortem arteriograms made after injecting a suspension of barium sulfate (250 Gm. to 500 cc. of water) into the pulmonary arterial system.

These arteriograms indicate that there was in each case a definite relationship between the condition of the artery and the location and formation of the thrombus. In every case the occluded artery was that vessel which was most damaged by anthracosilicosis or by pulmonary tuberculosis or by both.

The next important factor in the production of the thrombi appeared to be myocardial degeneration, with the resultant circulatory stasis within the lungs. Hypertrophy and dilatation of the right auricle and ventricle of the heart constitute a common finding in anthracosilicosis with or without pulmonary tuberculosis. During the past three years some 70 patients with anthracosilicosis came to necropsy at the White Haven Sanatorium. In every case there was some evidence of hypertrophy and dilatation of the right side of the heart. These cardiac changes were probably brought about by diffuse pulmonary arteriosclerosis, which is a common finding in anthracosilicosis, and by pulmonary emphysema, which is almost always present in anthracosilicosis.

That pulmonary circulatory stasis occurs in association with anthracosilicosis was established by studying the velocity of the pulmonary circulation in 45 cases of this disease, using decholin and ether. The pulmonary circulation time, which normally is from seven to twelve seconds, was prolonged in the majority of the cases. In 4 cases of thrombosis of the pulmonary artery the pulmonary circulation time was studied and found to be prolonged.

Two cases in the present series were instances purely of tuberculosis, without anthracosilicosis. Cardiac hypertrophy and dilatation are infrequent in cases of pulmonary tuberculosis, and the pulmonary circulation time is normal, as found in studies of 25 tuberculous patients. However, in these 2 cases there was both clinical and pathologic evidence of myocardial degeneration. The diseased lungs showed marked diffuse sclerosis of the pulmonary arteries in which thrombosis occurred.

The outstanding clinical features in the 9 cases of thrombosis of a branch of the pulmonary artery were: increasing dyspnea and cyanosis, most marked in the face; engorgement of the cervical veins; pain in the chest or in the epigastrium; restlessness and mental confusion; blurred vision; exophthalmos; low pulse pressure with a thin, thready pulse and, in the terminal stage, edema of the ankles. When the occluded vessel was a branch of the main branch of the pulmonary artery supplying a lobe, dyspnea and cyanosis were not marked. On the other hand, when the involved vessel was a main branch of the pulmonary artery, the symptoms were proportional to the completeness of the occlusion. In 2 cases the

involved lung was completely hollowed out from the apex to the base, having practically no pulmonary tissue, yet the thrombosis of the branch of the pulmonary artery going into this shell-like structure produced most acute dyspnea, cyanosis and pain in the chest. A question is raised whether the symptoms were not in part due to a sympathetic reflex spasm.

A New Instrument for Testing the Condition of the Myocardium at Autopsy: A Myocardiometer. David B. Fishback.

Death due to myocarditis, or true inflammation of the heart, is comparatively infrequent, whereas myocardosis or myocardial degeneration is found in most cases in which an autopsy is made. When death is not due to a cardiac cause, the heart may be only slightly degenerated. When death is due to a cardiac condition primarily, it may be explained on the physical basis of an intrinsic mechanical effect, congenital or acquired, such as marked valvular stenosis, regurgitation or a congenital anomaly, or on the basis of the decline in propulsive power of the heart due to marked softening and degeneration of the myocardium itself. When parenchymatous degeneration is advanced, the heart is very soft and friable. The more degenerated the heart muscle, the softer and more friable it will be. In fatty degeneration of the heart, friability reaches an extreme degree, the wall being easily pinched through.

Readings Obtained with the Myocardiometer in Small Series of Cases

Cardiac Condition	Cases	Myocardiometer Reading, Gm.
Normal (cases of accidental death, etc.)	5	1,800
Slight degeneration	31	1,300-1,800
Moderate degeneration	58	900-1,300
Marked degeneration	38	600- 900
Very marked degeneration	13	Below 600

I have devised an instrument to measure the amount of force required to perforate a portion of myocardium. The more degenerated the myocardium, the less is the force required, and hence the lower the reading of the instrument will be. The less degenerated the myocardium is, the more the force that is required to perforate it, and the higher the reading will be. Marked localized fibrosis would interfere with the accuracy of this test for degree of myocardial degeneration. Large areas of localized fibrosis are usually due to disease of the coronary arteries. Therefore, to perform the test in the heart, the center of the interventricular septum is chosen because this area is least likely to show local changes due to such disease. Postmortem changes play but a negligible part in the heart muscle from the standpoint of consistency. Examination of a heart removed from the body four hours after death and examination of this heart again eight hours after death showed exactly the same myocardiometer reading of 700 Gm. In a case of hypertensive heart disease with failure, the temperature of the myocardium twelve hours after death was 86 F., and the myocardiometer reading was 800 Gm. Thirteen hours after death, the temperature of the myocardium was 79 F., and the myocardiometer reading was 800 Gm. Fourteen hours after death, the temperature of the myocardium was 75 F., and the myocardiometer reading was slightly above 800 Gm. Autopsies done from thirty-six to forty-eight hours after death gave the usual myocardiometer readings, depending on the degree of degeneration.

The instrument is rust proof. It consists of two brass cylinders, one telescoping within the other. Inside is a brass spring. At one end of the spring is a plunger for penetrating the heart muscle, and at the other end is a rod resting against an indicator. After the plunger has completely pierced the cardiac muscle, the spring recoils, the rod drops back, but the indicator remains in position. The readings are from 0 to 2,000 Gm., mounting by 100 Gm. at each subdivision of the scale, e. g., 200, 300, 400, 500 and so on.

The accompanying table gives readings obtained with this instrument in several small series of cases. The four grades of myocardial degeneration are largely arbitrary, since it is difficult to draw a sharp line of demarcation between degrees of degeneration.

Histologic examination of sections of the hearts from the sites tested corroborated the readings as to degree of myocardial degeneration, in most cases.

BAXTER L. CRAWFORD, *President*

Regular Meeting, Feb. 10, 1938

HERBERT L. RATCLIFFE, *Secretary*

MASSIVE PAPILLOMAS OF THE URINARY BLADDER. STUART LIPPINCOTT.

The case of this 53 year old white man is interesting. Twenty years ago he had pain in the back, with hematuria. After that he had two or three attacks of hematuria yearly. The illness in question became noticeable about one year prior to death. The most persistent complaints at the time of examination were slight loss of weight and energy, swelling of the ankles of three months' duration,

Bladder showing five papillomas (three-fourths actual size).

dribbling of urine of one year's duration, nocturia two to three times a night of ten years' duration and cloudy urine, which had been observed for three years. The essential finding on catheterization was that bits of tissue became disengaged from the bladder; the condition was diagnosed from this tissue as grade 1 carcinoma of the bladder. The specimen of urine obtained by catheterization showed albumin and great numbers of red blood cells. The prostate was firm

and slightly enlarged. Laboratory study showed 2,700,000 red blood cells, a hemoglobin content of 54 per cent and 8,800 white blood cells. The carbon dioxide–combining power of the blood was 15 volumes per cent terminally, and during the last two weeks the blood urea nitrogen rose from 46 to 155. The urogram disclosed no semblance of a normal contour of the bladder. The entire organ was disfigured by a diffuse infiltrative process. Metastases were not found. At autopsy there was dilatation of the right side of the heart, with passive congestion of the lungs. Of chief interest was the bladder. It was heart shaped, with the fundus ballooning above the brim of the pelvis and narrowing as it approached the urethral orifice. The wall of the bladder was more than a centimeter thick; the mucosa was gray and trabeculated. In the posterolateral portion there were five pedunculated masses (figure), the stalks of which were firm, while the distal parts were masses of soft, grayish red material. The smallest mass measured 3 cm. in diameter and the largest 7 cm. They tended to fill the greater part of the lumen. There was no marked obstruction of the ureters, but there was bilateral pyelonephritis. Numerous sections showed typical villous papilloma (grade 1 carcinoma) with recent invasion of the blood vessels within the muscular layers; metastases were not found.

COMMON FORMS OF PNEUMONIA IN INFANCY: STUDIES BASED ON SECTIONS OF WHOLE LUNGS. IRVING GRAEF.

The observations at necropsy in 153 cases of pneumonia at the Bellevue Hospital during the past seven years are presented. In all, 220 cases were subjected to a method of study in which sections of a whole lobe or a whole lung were prepared from paraffin blocks. A technic has been devised which makes it possible to cut such large sections so that they will be between 8 and 12 microns thick. The group of 153 cases represented the common forms of pneumonia encountered; 44 of the remainder did not represent any form of pneumonia, and 23 represented rare forms of pneumonia.

This work was undertaken at the suggestion of Dr. Charles Hendee Smith, director of the children's medical service of the Bellevue Hospital, and has been done in collaboration with him and with Dr. Elizabeth T. Andrews. The clinical correlations and findings are being prepared for later presentation.

The whole lung section method was developed when it was realized that correct anatomic diagnosis was almost impossible when one dealt with an infant's lungs in which mixed inflammatory reactions combined to obscure anatomic markings. Further, small, random sections from obvious lesions fail to reveal the complete pathologic picture in the lung.

The common forms of pneumonia are classified as (1) lobular pneumonia, (2) "simple" bronchopneumonia, (3) broncholobular pneumonia and (4) "lobar" pneumonia.

Lobular Pneumonia.—The cases of lobular pneumonia numbered 70, and in these the characteristic lesion appeared to be a consolidation due to a variable hemorrhagic or fibrinopurulent exudate in the involved lobules. Bronchiolar involvement was limited to endobronchial erosion and inflammation in the affected lobules. There was irregularity in the distribution of the lobular involvement, with an especial tendency to affect the lobules around the hilus, and in the density of the exudate. Foreign materials, consisting of amorphous eosinophilic débris mixed with bile salts, sometimes with lipids, were regularly found in the bronchioles and in the alveolar spaces. In some cases bronchiolar abscesses developed around eroded bronchioles. Often aspiration appeared to be a terminal event, as the foreign material was sometimes found in the alveoli or the bronchioles unattended by reaction. In some cases a necrotizing type of inflammation was seen, with large central zones of necrosis surrounded by zones of hemorrhage. Later, abscess formation was marked.

Analysis of this group showed that this form of pneumonia is commonly found in infants in the first month of life, especially in the prematurely born, weak or congenitally defective infants who have required forced feeding. Fever and infec-

tion of the upper part of the respiratory tract (by this is meant evidence of nasopharyngitis, otitis media or both) are rare in infants under 1 month of age. Other cases were found in children between 1 month and 12 months of age, and in these the disease was usually febrile and associated with an infection of the upper part of the respiratory tract. Nevertheless, there was evidence of aspirated foreign material in these infants to the same extent as in the younger group. Lobular pneumonia is often unsuspected during life and may occur as a terminal event, especially in debilitated infants. But in 53 of the 70 cases it was regarded as the primary cause of death. The relative infrequency of pleural and interstitial inflammation, the high frequency of the aspiration of foreign material and hilar involvement are the outstanding features of this group.

"Simple" Bronchopneumonia.—This disease is found comparatively rarely at necropsy inasmuch as there were only 6 cases in the entire group. The condition is characterized by bilateral diffuse inflammation of the bronchial system, with catarrhal inflammation of the bronchial mucosa and engorgement of the bronchial vessels, and a striking infiltration of the walls and outer layers of the bronchi and bronchioles by mononuclear cells. One may find a few mononuclear cells, desquamated cuboidal epithelium and little fibrin or edema fluid in a few of the alveoli immediately contiguous to the inflamed bronchi or bronchioles. There is a tendency toward collapse round the involved bronchi or in areas supplied by them when the lumen is compressed. The involvement of the alveoli is scanty, and for this reason the term "simple" is applied to the bronchopneumonia in these cases. The association with infection of the upper part of the respiratory tract is notable, and there is no evidence of the aspiration of foreign material, of pleuritis or of septal inflammation.

Broncholobular Pneumonia.—This term is used to describe two characteristic lesions in the lung: One is inflammation of the bronchial system like that seen in "simple" bronchopneumonia; the other is extensive suppuration or exudation involving whole lobules irregularly or, in some cases, in a confluent manner to include the major part of a lobe or several lobes. This type is a mixed pneumonia and is uneven in its distribution. The lesions are disseminated; varying degrees of lobular involvement are found in the different lobes or even in the same lobe. Collapse is a prominent feature. In contrast to the simple forms of bronchopneumonia, widespread inflammation of the interlobular septums and of the pleura and abscess formation are common. Aspiration of foreign material may be one mode whereby inflammation of the lobules is caused in patients with "simple" bronchopneumonia, and it was present in 13 of 52 cases of broncholobular pneumonia. Antecedent or concomitant disease of the upper part of the respiratory tract is the rule, and fever attends the clinical course. None of these patients were under 30 days of age, and no fatality was encountered in the third year of life. This form is often complicated by evidence of infection elsewhere in the body and is therefore sometimes not the sole cause of death. Chronic processes are encountered in which the peribronchial infiltration becomes marked, and there may be squamous metaplasia of the lining epithelium. Organizing endobronchiolitis with fusion of the exudate to the bronchial walls was also found. Bronchiectasis is another late complication and may persist while the lobular lesions, if any, disappear.

"Lobar" Pneumonia.—The last group consists of 25 cases in which massive consolidation of one or more lobes was present. These have been divided into three groups. The first consists of 13 cases in which there were massive uniform inflammation and consolidation; the second consists of 10 cases in which there was massive consolidation characterized by necrosis, hemorrhage and abscess formation, and the third includes 2 cases in which there was massive consolidation due to the aspiration of foreign material (cod liver oil in one and all feedings via a tracheoesophageal fistula in the other). The high frequency of involvement of the right lung, especially of the right upper lobe, was notable.

In the cases in which there was massive uniform involvement, the lesion resembled that ordinarily encountered in pneumococcic pneumonia in the adult

patient and was striking for its homogeneity throughout the affected lobe or lobes. Pleuritis and septal lymphangitis were common in the entire group. Clinically, the cases were characterized by a stormy febrile course and antecedent infection of the upper part of the respiratory tract. Peribronchial inflammation was encountered in 19 cases. In 14 it was limited to the consolidated lobe; it may have followed the alveolar lesion as a secondary process. In 5 cases it was bilateral and apparently independent of the alveolar lesion. This has suggested that in some cases bronchopneumonia has preceded lobar pneumonia and that in others it may have followed it. The cases in which the bronchial inflammation was limited require further study. The distribution of these cases according to age indicates that lobar pneumonia may occur throughout infancy.

EXPERIMENTAL GLOMERULAR NEPHRITIS. WILLIAM E. EHRICH.

An attempt has been made to show that the acute phase of the nephritis produced by the method of Masugi is identical with the corresponding phase of glomerular nephritis of man, and that by this method new light is thrown on the pathogenesis of the disease. Ducks were immunized with the juice of the kidneys of rabbits, and the antikidney serum thus obtained was injected intravenously into rabbits. In animals killed on the sixth day or thereafter, the kidneys were swollen and showed fine dots of blood on their surfaces. The main histologic change was marked enlargement of all the tufts, due to a proliferation of their cells. In addition there was deposition of fibrin in the glomerular spaces and later, as a result thereof, the development of adhesions, crescents and complete fibroses. Both changes appeared at the end of the first week. But whereas the proliferation was present in all glomeruli in all animals studied, the deposition of fibrin and the development of crescents were found only in about half of the animals and in these only in a varying percentage of the glomeruli. It follows, therefore, that crescents are not a feature essentially characteristic of a certain phase of glomerular nephritis but must be regarded as a complication which probably aggravates the disease. Other histologic features were erythrocytes in capsular spaces and tubules, hyaline casts, hyaline droplets in convoluted tubules and in a few cases fatty degeneration. Clinical observations included edema, albuminuria, hematuria, oliguria, diminished filtration and rise in blood urea nitrogen. During the first week of the experiment there was excellent diuresis, with an increase in filtration, while the glomeruli were rather hyperemic. Oliguria, decrease in filtration and ischemia of the glomeruli became manifest only after eight days, when the anatomic changes were fully developed. It is believed, therefore, that glomerular nephritis starts with a period of latency and that it does not start with a spastic condition in the kidney, as maintained by Volhard. As to the further course of the disease, not much can be said at present. But it appears to be certain that at least the milder lesions heal completely.

HERMAPHRODITISM: A NEW CONCEPTION. JAMES F. MCCAHEY.

At the present time hermaphroditism is classified as (1) true hermaphroditism, in which the gonads are intersexed, and (2) pseudohermaphroditism, which may be either of the female type, i. e., ovaries normal but associated with the external conformation of the male, or of the male type, with testes present but associated with the external appearances of the female.

Explanations of these malformations are based on certain embryologic conceptions, of which the most important are: 1. The primary gonad is identical in both sexes and may form either an ovary or a testis. 2. If an ovary develops the müllerian system forms the female genital organs; if a testis develops, the wolffian system forms the male genital organs. 3. The endocrine action of the ovary or of the testis inhibits the differentiation of the genitalia of the opposite sex.

Present day management of hermaphroditism is based on this explanation, but the therapy is unsatisfactory because of uncertainty as to the proper procedure

in any given case. And it appears that the basic conception of the condition has been erroneous. For in both sexes the primary gonad is testicular. In the male it develops directly into a testis, but in the female the cortex of the ovary grows around it, compressing it into the medulla so that it remains vestigial under ordinary circumstances. If this primary gonad is stimulated experimentally, intersexuality may be produced in the female.

Analysis of cases that have been described indicates that true hermaphroditism always occurs in persons who are genetically female, that the müllerian derivatives are least affected by abnormal testicular endocrine action and that the most marked effects are on the external genitalia, which are formed from the urogenital sinus. Also persons presenting female pseudohermaphroditism show more marked somatic intersexuality than do those with true hemaphroditism even though the ovaries of the former are considered normal. Careful examination of these ovaries probably would reveal male elements, since male interstitial cells have been found in sections of ovaries of normal persons and primary testicular cords in the ovaries in a case of virilism. In addition, study of cases of male pseudohermaphroditism indicates no development of the müllerian system. The so-called "feminine" somatic manifestations may be due to an insufficiency of testicular hormone, a condition which in many cases is secondary to dysfunction of the hypophysis, the pseudovagina seen in such cases representing the remains of the urogenital sinus.

NEW YORK PATHOLOGICAL SOCIETY

N. Chandler Foot, *President*

Anniversary Meeting, Jan. 27, 1938

Milton Helpern, *Secretary*

Ovarian Adenoma Associated with Masculinization: Hypernephroma vs. Luteoma. Antonio Rottino.

A Puerto Rican 20 years of age appeared at St. Vincent's Hospital, in the outpatient department, in February 1934, with an amenorrhea of nine months' duration. She had an increased growth of hair about the entire body, particularly on the face. This hirsutism had made its appearance six months after the onset of the amenorrhea. She next presented herself on May 25, 1937, with renal colic, which cleared up in a few days. The amenorrhea had persisted. The hirsutism had grown more marked, so that she shaved daily. Her voice had become deeper, and the clitoris was enlarged. Of interest are the results of assays of the urine: estrogen, 3.3 rat units per liter; androgen, two specimens, 17.3 and 15.7 international units, respectively. On June 10, an enlarged right ovary was removed. Within a month the menstrual periods had returned, and the hirsutism gradually diminished, so that by December 1937 she shaved only once in two weeks.

The specimen consisted of an orange-colored nodule measuring 3 by 2.5 by 2.5 cm., which was completely encapsulated by thinned-out ovarian tissue. The tumor was composed uniformly of large, more or less polyhedral cells with distinct cell borders, containing an abundance of lipoid. They appeared so much like cells of the zona fasciculata of the adrenal gland that several observers (Meyer; Novak; Schiller) labeled the tumor hypernephroma with origin in an adrenal rest. Others (Vines; Frazer) believed that the tumor looked more like luteoma. That there have been cases in which tumor of the adrenal cortex was associated with masculinization lends significance to the fact that the tumor in question histologically resembled adrenal cortex. This may, therefore, bespeak an origin from ectopic adrenal tissue. One must not forget, however, the rarity of an adrenal rest in the ovary in contrast to its more frequent presence in the region of the ovary. Regardless of differences of opinion concerning its histogenesis, one can

be sure that the growth in this case belongs to a group of rare masculinizing ovarian tumors different from arrhenoblastoma.

DISCUSSION

WALTER SCHILLER (by invitation): I have had the opportunity to examine specimens, slides and special stains of more than 25 masculinizing ovarian tumors. It is clear that such tumors can be divided into two groups: One is arrhenoblastoma, and the tumors of this group are so characteristic that one cannot make mistakes in their diagnosis once it is realized that arrhenoblastoma is nothing but a neoplasm which duplicates the fetal development of the male gonad but without spermatogonia. Arrhenoblastoma may be easily classified into mature and immature forms. Much more complicated is the second group. I succeeded in getting hold of the slides of the tumors observed by Sellheim, Cosacesco and Bovin. The only tumor which escaped me was that reported by Schultze-Bingel, from which no slides or specimens were preserved, as the patient was operated on during the war. The case reported by Tuffier was complicated by tumors of the adrenal glands, which probably caused the masculinization. The ovarian tumor might have been only accessory and had no relation to the masculinization. In addition to these I have seen in Vienna slides of a tumor which was recently reported by Novak and Wallis and of a similar one observed in San Francisco, a report of which was published by Maxwell; so I have had in my hands the material of almost all the tumors of this peculiar type that have been reported. A characteristic feature of these tumors is that the cells are sharply demarcated. They have clearcut walls like those of true epithelial cells. The suggestion that they are granulosa cells does not hold as soon as one considers the character of the cells and compares them with real granulosa cells. The latter are of mesenchymatous origin and never lose their mesenchymatous character. Whenever one sees granulosa cells, they form a syncytium. The single cells are never sharply demarcated from each other by walls. They are connected by fibers, described and investigated by Cook and Ikeda, which pass from one cell to the next. These fibers are absolutely characteristic for the cells of a corpus luteum. Never in the granulosa of a corpus luteum does one find marked cell boundaries, whereas marked boundaries, are characteristic for the cells of hypernephroma. I have had an opportunity to compare these ovarian tumors with numerous hypernephromas and found a great similarity. In addition, I think there is no reason to accept the hypothesis that because a tumor produces estrogenic substance it should have the capacity of masculinizing the bearer, whereas, on the other hand, according to Julius Bauer, one may accept the theory that hypernephromas, because they have a tendency to support remnants of characters of the opposite sex, may masculinize a woman or feminize a man. I have seen testicular tumors of exactly the same structure. Two of the latter clinically caused feminization of the bearers, so that once such tumors have been characterized as hypernephroma this classification harmonizes with the cytologic findings as well as with the physiologic conception which one has come to entertain of hypernephromatous tissue.

S. MILTON RABSON: About nine years ago Erdheim in an autopsy in Vienna encountered a circumscribed tumor of the ovary. He sent it to Kermauner, who sent back the diagnosis of "theca-luteoma." That patient showed no unusual signs at autopsy.

SEATON SAILER: Were any stains for reticulum cells made on this tumor?

WALTER SCHILLER: I had the opportunity to speak with Kermauner about this case and he said, "The best I can do is to say that it is a luteoma, but I am not convinced of this classification."

ROBERT A. MOORE: Have assays for androgen been reported in any of the cases recorded in the literature?

ANTONIO ROTTINO: A stain for reticulum was made. Reticular fibers were found extending from the perivascular connective tissue to surround individual tumor cells and masses of tumor cells.

In reply to Dr. Moore, in the cases reported no such assays were done.

CYSTIC LYMPHANGIECTASIA OF THE ADRENAL. S. MILTON RABSON and (by invitation) EDWARD F. ZIMMERMAN.

This article will be published in full in a later issue of the ARCHIVES OF PATHOLOGY.

THREE INTERESTING CASES OF CARCINOMA ARISING IN THE BILIARY TRACT. LOUISE H. MEEKER and (by invitation) GEORGE SAYPOL.

The first patient was a man aged 46 in whose case preoperative diagnosis of carcinoma of the ampulla of Vater was followed by removal of a carcinoma approximately 10 mm. in diameter, by the surgical technic of Whipple, Parsons and Mullins. The patient remains well four months after the operation.

The second patient was a woman aged 40 with carcinoma of the neck of the gallbladder and metastases in both ovaries. The chief interest is surgical, as the case suggests the importance of examining the gallbladder when an unexplained Krukenberg tumor is found at operation and, on the other hand, examination of the pelvis when carcinoma of the biliary tract is recognized. In this instance the primary tumor was first recognized at necropsy.

The third patient was a woman aged 64 in whom a surgical exploration disclosed scirrhous carcinoma of the gallbladder (neck?) with secondary involvement of the base of the appendix. The pathway of metastasis, whether by lymphatic extension or by implantation through the intestinal lumen, remains uncertain. The patient survived the operation only a few months, and there was no necropsy.

ULCERATION OF THE PERITONEUM (CHEMICAL?). LOUISE H. MEEKER and (by invitation) JOSEPH M. GANNON.

Ulceration of the peritoneum of the pouch of Douglas was disclosed at necropsy in a youth aged 16, who died in cardiac decompensation following rheumatic fever of six years' duration. A mercurial diuretic (2 cc. of salyrgan diluted in 25 cc. of physiologic solution of sodium chloride) had been administered by intraperitoneal injection ten weeks before death. Biospectrometric analysis of the tissues of the floor of the ulcer did not reveal the presence of mercury.

DISCUSSION

JOHN MURRAY STEELE (by invitation): This appears to me to be of rather extraordinary interest. Local lesions from salyrgan of a nature much like this have been described from time to time, even when the drug has been given as deeply as in the muscle tissue, where it is supposed to be readily absorbed. Such lesions occur more frequently if the needle has not penetrated into the muscular tissue, the drug having been given subcutaneously. I do not know of any previous report of a death occurring in a short time after an intraperitoneal injection of salyrgan. Since the solution of salyrgan is of considerable weight, one may easily imagine that it would collect in the lower part of the peritoneum, particularly in a patient with dyspneic, orthopneic cardiac disease who is in the semiupright position. This is perhaps just one more reason for employing mercurin with theophylline, the application of which seems to be unaccompanied by any form of necrosis, even when it is injected in large amounts into the subcutaneous or fatty tissues. The extraordinary fact is that mercury was not found in the abscess or in the region about it. When salyrgan is injected deep into the tissues and the injection results in the development of a local sterile necrotic abscess, mercury can usually be found in the local tissues.

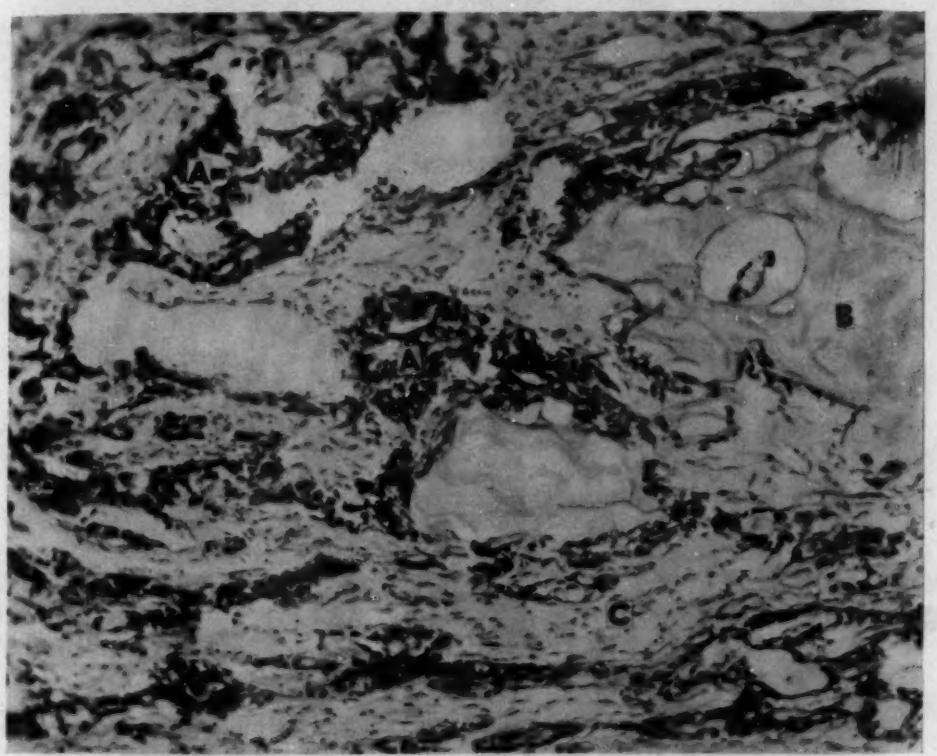
N. CHANDLER FOOT: In examining the sediments from serous fluids in our laboratory, my associates and I have noted that there are regularly large numbers of peritoneal cells in the exudates both from the peritoneum (in cases of cirrhosis) and from the pleura (particularly in cases of failing heart), and in one of these cases, encountered when we began making these examinations, we were fairly sure that there was carcinomatosis of the peritoneum. When the patient died and came to autopsy, no carcinoma was found, but there was an area in the pouch

of Douglas similar to the one Dr. Gannon has just described, covered with a loose layer of fibrin. On microscopic examination, an extensive proliferation of peritoneal covering cells was noted. Whether that patient had had salyrgan or mercurin with theophylline I do not know, but I am fairly sure that one of these preparations had been given.

J. M. GANNON: I should like to emphasize the fact that we do not believe that the patient's death was related to the ulceration of the peritoneum.

METASTATIC CARCINOMA OF THE APPENDIX, COMPLICATED BY ACUTE GANGRENOUS APPENDICITIS AND PERFORATION. LOUISE H. MEEKER and S. R. WEINBERG.

A man of 87 years suffered from progressive constipation for four months before his admission to the hospital. Associated with this complaint there were generalized



Adenocarcinoma of the pancreas in a man aged 87: *A*, deep-staining epithelial cells arranged in ducts and nests; *B*, mucinous degeneration; *C*, dense connective tissue stroma.

weakness and a loss of 15 pounds (6.8 Kg.) in weight. At first he was able to defecate after taking mild cathartics, but later his obstipation could not be relieved by such measures. Four days before admission he took a large dose of mild mercurous chloride, and a few hours later he had a scanty bloody stool, followed by violent vomiting lasting many hours.

When he was examined in the hospital his abdomen was markedly distended by fluid. In the rectum a large firm mass was felt above the prostate. A diagnosis

of carcinoma of the rectosigmoid was made. Sigmoidoscopic examination revealed the mass at the rectosigmoid junction. The mucosa of the rectum was thinned and reddened but not ulcerated. A day later the patient became critically ill and died in coma.

At necropsy, 5,500 cc. of turbid yellow fluid filled the peritoneal cavity. The peritoneum was reddened and covered with a flaky fibrinous exudate, and numerous metastatic nodules were found all over the peritoneum. Frank pus was seen escaping from a perforation in the posterior aspect of the appendix, 0.5 cm. from the tip. Ten centimeters from the anal orifice there was a wedge-shaped scirrhous neoplasm, extending from the anterior wall of the rectum to the prostatic capsule. The prostate and seminal vesicles, however, were not involved.

There was a similar large firm mass in the head of the pancreas, 6 cm. in diameter. This tumor was retroperitoneal, but the common bile duct was not encroached on. The body of the pancreas was not involved, but the peripancreatic lymph nodes about the tail of the pancreas were so enlarged and so matted together by metastatic invasion that another mass of similar size was formed.

The liver was studded with metastatic nodules, the largest 10 cm. in diameter. Microscopically, the tumors of the pancreas were partly scirrhous and partly mucinous adenocarcinoma of duct cell type, evidently primary to the pancreas. The cells of the neoplasm were polyhedral and had deep-staining nuclei and eosinophilic cytoplasm. Mitoses were fairly numerous. The malignant cells were embedded in a dense fibrous tissue stroma in some areas (figure) and in other areas formed alveoli varying in size, some of them dilated and filled with mucinous exudate.

The same structure and type of neoplastic epithelium formed the perirectal tumor, indicating its origin from the primary tumor of the pancreas and establishing its metastatic character. This finding contradicted the clinical diagnosis of a primary tumor of the rectum.

The other metastatic tumor growths, in the liver and in the peritoneum, were of similar structure. There were identical metastases in the omental adhesions attached to the proximal two thirds of the appendix and in the muscular layers of the appendix. There was an associated severe, gangrenous appendicitis with rupture. The mucosa was destroyed by the inflammatory process, and throughout the partly viable muscular and connective tissue coats of the appendix there was a dense infiltration by polymorphonuclear neutrophils and lymphocytes (muscle fibers were demonstrated by the Van Gieson method).

General Observations on the Serum Therapy of Infections with Streptococcus. Adele E. Sheplar (by invitation), Martha Jane Spence (by invitation) and Ward J. MacNeal.

Following a previous report of 26 cases, there is now presented a brief discussion of 66 additional cases of grave streptococcic infection in which the patients were treated with serum. There were 18 deaths, of which 6 were from diffuse bacterial meningitis and 2 from generalized peritonitis. In only 3 of the 18 patients who died was the effect of the serum really disappointing. Five of the 48 instances of successful treatment are discussed as examples of treatment with three different preparations of streptococcus serum and of serum therapy in combination with multiple transfusions, with bacteriophage and with sulfanilamide, combinations which seem promising.

This paper will appear in the *Archives of Surgery*.

Further Observations on Bacteriophage Action in the Presence of Blood. Ward J. MacNeal, Margaret A. McRae (by invitation) and Rudolf A. Colmers (by invitation).

Experimental studies in vitro have shown that the presence of blood or of blood serum interferes with the dissolution of bacteria by bacteriophage. D'Herelle

found, however, that bacteriophage in watery solution exerts a marked opsonic effect, and these observations have been confirmed and extended by George H. Smith. Nelson observed that bacteriophage intravenously injected increases to a marked degree the phagocytic activity of the wandering leukocytes for the phage-susceptible bacterial strain during a period from one to six hours after the injection of the bacteriophage. MacNeal, Frisbee and Slavkin observed increased phagocytic activity of the fixed endothelial cells, particularly in the liver and spleen, after intravenous injection of bacteriophage.

In the present study, exposure of susceptible bacteria to bacteriophage for a few minutes rendered them more susceptible to phagocytosis, and this opsonic effect was not inhibited but apparently favored by the presence of blood serum in the test tube. This opsonic effect could also be demonstrated in the blood of experimental animals during the first hour after intravenous injection of bacteriophage.

This paper will appear in full in the *Journal of Infectious Diseases*.

PHAGOCYTOSED STAPHYLOCOCCI IN THE CIRCULATING BLOOD (SLIDE DEMONSTRATION). E. H. PAHL (by invitation) and WARD J. MACNEAL.

An ordinary film of blood taken from the finger of a patient about twelve hours before his death showed staphylococci within many of the polymorphonuclear neutrophilic leukocytes. Blood cultures made at the same time yielded more than 5,000 colonies of Staphylococcus aureus per cubic centimeter of blood. At necropsy there were large active vegetations on the heart valves. These phagocytic cells have been pictured in the *Journal of Bone and Joint Surgery* (**19**:902, 1937 [fig. 23]).

DIFFERENTIALLY STAINED PARTICLES WITHIN BACTERIA UNDERGOING LYSIS BY BACTERIOPHAGE (SLIDE DEMONSTRATION). WARD J. MACNEAL and FRANCES C. FRISBEE (by invitation).

Centrifuged sediments of cholera cultures undergoing lysis by action of bacteriophage, stained by the technic of Castañeda, show minute granules which retain the blue stain. These granules are found within the swollen and distorted bacterial cells, and possibly they represent the bacteriophage particles. These pictures have been presented in the *Journal of Infectious Diseases* (**61**:224, 1937 [plate I]).

BUFFALO PATHOLOGICAL SOCIETY

ERNEST WITEBSKY, *President*

Regular Meeting, Jan. 29, 1938

SAMUEL SANES, *Secretary*

RING TEST FOR THE VAN DEN BERGH REACTION. NORMAN W. ELTON.

Van den Bergh discovered that some icteric serums, like bile, did not require the addition of alcohol to yield a red color with Ehrlich's diazo reagent. The terms "direct" and "indirect" are obsolete, for the latter concerns actually a quantitative determination of bilirubin, and there are numerous modifications of this technic. The direct is the van den Bergh reaction. Overlaying the serum with the reagent, instead of mixing them, is the essential procedure of the ring test. The zone of contact is so sensitive that the number of positive reactions detected is greatly increased and the use of the delayed reaction is practically eliminated. This supports the opinion of Hubbard and others that the delayed reaction with the original technic was closely related to the immediate reaction. The clinical

value of the technic was originally reported by me in 1931. In 1921 Lepehne mentioned the technic but missed its significance. In 1933 Magath advocated its general adoption. Its application in the study of various clinical entities disproves McNee's classification of jaundice, challenging especially the entire conception of "hemolytic jaundice." A new hypothesis of the mechanism of jaundice has been proposed for temporary use. The burden of proof that there is overproduction of bilirubin in the conventional "hemolytic" group now lies with the proponents of that concept.

THE MORGAN BACILLUS AS THE CAUSATIVE AGENT IN PERITONITIS. E. NETER and M. L. GOODALE.

In view of the fact that the pathogenic significance of the Morgan bacillus is not as yet generally accepted, a case of infection with this bacillus is presented:

A boy 11 years of age became acutely ill with symptoms of appendicitis. The following day he was operated on, and diffuse purulent peritonitis and severe appendicitis, with a small perforation at the tip of the appendix, were found. The appendix was removed and the pus aspirated. A smear of the pus showed many leukocytes and gram-negative bacilli. A culture revealed a pure growth of a nonlactose-fermenting, gram-negative bacillus, which revealed the following cultural characteristics: It grew well on ordinary culture mediums. It rendered litmus milk slightly acid after from one to two days' incubation at 37 C.; the milk became alkaline after from ten to fourteen days. It fermented the following carbohydrates, with production of acid and gas: dextrose, maltose, mannitol, galactose and levulose. It failed to attack, even after two weeks' incubation, lactose, sucrose and dulcitol. It did not liquefy gelatin. It produced indol within eighteen hours.

Agglutination tests were made with serums against all organisms of the typhoid-paratyphoid-dysentery group, but no agglutination was obtained. Cultures of the bacillus proved to be virulent for laboratory animals, killing mice and guinea pigs within twenty-four hours after intraperitoneal injection; the bacillus was recovered in pure culture from the cardiac blood. It corresponds to the Morgan bacillus, type 14.

In the literature cases are reported in which the Morgan bacillus caused disease of the urinary tract, mastoiditis, meningitis and septicemia. Hence, there is no doubt that the Morgan bacillus, similar to the colon bacillus, may cause various purulent infections. Its significance for intestinal diseases, however, is denied by some authors. It is for this reason that Thjøtta and others have listed the Morgan bacillus in the "colon bacillus group" rather than in the "salmonella group" as proposed in D. H. Bergey's "Manual of Determinative Bacteriology" (ed. 4, Baltimore, Williams & Wilkins Company, 1934).

AUTOAGGLUTINATION, PSEUDOAGGLUTINATION AND AUTOHEMOLYSIS. E. WITEBSKY, B. T. DAVIES and C. M. HILL.

Two blood specimens taken from different patients for the purpose of making blood cell counts showed definite autoagglutination. When kept at room temperature one showed a degree of agglutination that rendered the counting of cells impossible. In view of the fact that true autoagglutination is relatively rare, a thorough analysis was carried out in both cases. To find out whether we were dealing with autoagglutination or pseudoagglutination, increasing dilutions of the serums were set up in test tubes. Serum 1 agglutinated cells of group O as well as its own cells in dilutions up to 1:1,000; serum 2, in those up to 1:500. The titer in the first case was reached at temperatures up to 15 C., while that in the second was attained only when the serum was kept in the ice box. The degree of dilution showed that we were dealing in both cases with true autoagglutination and not with pseudoagglutination. Pseudoagglutination would disappear in serum dilutions of from 1:2 to 1:4.

Separation and isolation of the agglutinin were attempted and carried out in the following way: Twenty-five hundredths cubic centimeter of a suspension of red cells of group O were agglutinated by the addition of 1 cc. of autoagglutinating serum. The solid clump obtained was washed three times with ice-cooled physiologic solution of sodium chloride. It was then suspended in 1 cc. of the saline solution, kept in a water bath at 37 C., where the agglutination disappeared quickly, and centrifuged at 37 C. A clear supernatant fluid was obtained. This supernatant fluid yielded positive autoagglutination almost up to the same dilution as the serum itself, while the last wash water was entirely negative. The antibody solution induced agglutination of animal cells, such as guinea pig, rabbit and ox cells. Typhoid bacilli, on the other hand, were not agglutinated.

Some authors believe that autoagglutination is usually associated with blood dyscrasias. Our first patient, however, was suffering from lobar pneumonia and the second from camphor poisoning. Both recovered promptly. No changes were observed in the blood picture or in the chemical composition of the blood. The blood of the father of the first patient was examined but did not show signs of autoagglutination. Autoagglutination, therefore, is not necessarily connected with certain types of blood diseases. In a recent report (Koepplin, F.: *Ztschr. f. klin. Med.* **130**:784, 1936) autoagglutination was stated to have the same basis as autohemolysis. The Donath-Landsteiner test for autohemolysis was negative. The Wassermann reaction was negative in both cases, and there was no history of syphilitic infection. Autohemolysis, therefore, must be considered separately from autoagglutination and is due to an entirely different mechanism. These findings are in agreement with those in earlier investigations by several authors, for example, Clough and Richter (*Bull. Johns Hopkins Hosp.* **29**:86, 1918).

TUBERCULOUS REINFECTION IN YOUNG ADULTS WITH FORMATION OF TYPICAL COMPLEXES (RANKE) OF DIFFERENT AGE. KORNEL L. TERPLAN, E. C. KOENIG and HELEN SANDERSON.

Two cases are presented: The first is that of a 29 year old white man who died of peritonitis following rupture of the appendix; the other case is that of a 21 year old white woman who died of osteomyelitis of the frontal bone with subdural empyema. In both cases the study consisted of roentgen examination of the undissected lungs, including the tracheobronchial tree and the bronchial mediastinal lymph nodes, careful gross dissection, by means of which all focal lesions were detected, and histologic examination of these and of the regional lymph nodes.

The observations in the first case probably point to three different periods of tuberculous infection. In the lower lobe of the left lung there was an entirely ossified lesion, about lentil size, in the process of fragmentation into smaller bony particles. No tuberculous lesions were found in the lymph nodes draining this area: no calcification, no scars, no recent changes. These nodes were examined in complete serial sections.

The lower lobe of the right lung contained about seven completely calcified, mostly nodular foci in an area about 3 cm. in diameter. Histologically, these showed the typical picture of calcified tuberculous lesions. Only one, the smallest of the group, showed a thin bony ring. The lower tracheobronchial lymph nodes on the right contained three completely hyalinized and partly calcified conglomerate tubercles, about pinhead size.

The third lesion was in the upper lobe of the left lung. On gross inspection, there were seen a few hazelnut-sized cheesy foci in the upper third of the lobe, in the posterior subapical portion. These foci presented a somewhat infarct-like appearance. In addition, the entire group of lymph nodes regional to this part of the upper lobe showed extensive caseation with beginning cavity formation. These severe, caseated lesions were seen in the bronchial pulmonary lymph nodes at the hilus of the left upper lobe above the left major bronchus and in the left upper tracheobronchial group.

Epicritical analysis points to the bony lesion in the left lower lobe as the oldest tuberculous focus, which apparently remained restricted to the lung tissue. The calcified foci in the right lower lobe, one of which already showed beginning ossification, form with the hyalinized and partly calcified conglomerate tubercles in one of the tracheobronchial lymph nodes a typical tuberculous complex, apparently in a healed stage. The changes in the left upper lobe point to a relatively recent tuberculous infection, with formation of a massive cheesy lymph node complex. The histologic examination reveals clearly a marked difference in the structural age of the pulmonary foci in the three mentioned areas, which are quite separate, being in different lobes and on opposite sides—right lower, left upper and left lower lobes.

In the second case the left lung showed a closed calcified complex which consisted of: a pinhead-sized calcified tuberculous focus in the apex of the lower lobe, considerably ossified; close to this focus a slightly calcified subpleural lymph nodule; a few slightly calcified bronchopulmonary lymph nodes and one slightly calcified upper tracheobronchial lymph node regional to the primary focus.

In the lower lobe of the right lung a large pea-sized cheesy focus was found with extensive caseation of the right bronchopulmonary and lower tracheobronchial lymph nodes and a few pinhead-sized subpleural tubercles in the parenchyma of the lung surrounding the cheesy focus. Complete histologic analysis of all the foci in the lung and of the lesions of the lymph nodes revealed again in this case a distinct difference in the structure of the two complexes: that in the left lung was an apparently healed, stony, calcified complex, with ossification of the primary focus; that in the right lung, in the lower lobe, was a caseated focus, with cheesy changes in the regional nodes. In the latter case hematogenous spread to the liver had occurred, with development of a few fibrous cheesy tubercles.

Both cases demonstrate clearly that true reinfection may form an entirely typical tuberculous complex, just like that of primary tuberculous infection.

CHICAGO PATHOLOGICAL SOCIETY

FRANCIS D. GUNN, *President*

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EDWIN F. HIRSCH, *Secretary*

PATHOLOGIC EFFECTS IN POISONING FROM ELIXIR OF SULFANILAMIDE. PAUL R. CANNON and E. M. K. GEILING.

The poisonous effect of elixir of sulfanilamide is due to the diethylene glycol which is used as a solvent. This material when excreted through the kidneys causes severe hydropic degeneration of the convoluted tubules and occlusion of the lumens of the latter. Anuria results, followed by acidosis, uremia and in many instances death. Diethylene glycol in toxic doses also causes characteristic central hydropic degeneration of the liver. These changes in the kidney and liver were observed in material from 11 fatal cases of poisoning from elixir of sulfanilamide and in material from dogs, rabbits and rats given toxic doses of diethylene glycol or of elixir of sulfanilamide. In both the animals and the patients there also developed pulmonary edema and in some bronchopneumonia.

In several of the patients whom we have studied, cortical necrosis with hemorrhage was present, resembling in many respects the symmetrical cortical necrosis seen in some cases of so-called toxemia of pregnancy. We have seen hyaline thrombosis of the smaller cortical arteries and arterioles, with resulting diffuse infarction of the cortex.

Diethylene glycol is a hygroscopic agent, and it may accumulate in the cells of the convoluted tubules, causing them to hold more water. On the other hand, its effect may be due to its injuring the cytoplasm of these cells, with resulting disturbance of their internal metabolism and the development of severe intracellular edema. Sulfanilamide alone does not cause these effects in dogs, rabbits or rats even when given in large doses.

MALFORMATIONS: A STUDY OF TRENDS WITH RESPECT TO GEOGRAPHIC REGIONS AND WITH RESPECT TO SEX. WILLIAM F. PETERSEN.

Previous studies demonstrated that the ratio of the number of infants who die from malformations to the number of normal newborn infants is higher in the northern states. The annual trends of this ratio in a group of states were then investigated. From 1900 to 1935 the ratio varied from year to year, but identical trends were noted for different regions, i. e., for the New England group, the North-Central group, the middle Atlantic group, the Plains group, and so on. Apparently these regional trends reflect environmental conditions that in turn influence the maternal organism during the early stages of gestation. Incidental thereto, attention is called to the fact that the sex ratios for different types of malformations reveal marked differences. With malformations due to early interference (e. g., a lesion of the central nervous system), there was a low ratio of from 0.5 to 1, while with malformations presumably due to late interference (gastrointestinal, genitourinary, cardiac) a ratio of from 1 to 4 was found.

The observations tend to support the suggestion of Mall that these lethal malformations are due to early environmental disturbance. Apparently, they are not caused by the chance mating of individual carriers of recessive genetic faults.

CYST OF THE HEART. ISRAEL DAVIDSOHN.

This article will be published in full in the July issue of the ARCHIVES OF PATHOLOGY.

NEUROEPITHELIOMA OF THE CEREBELLUM. EDWIN F. HIRSCH and ERIC OLDBERG.

Bucy and Muncie in 1929 reviewed the published descriptions of neuroepithelioma of the brain and concluded that their report was the fifth authentic account and the second of neuroepithelioma of the cerebellum. Those subsequently summarized by McLean and Lentiere in 1936 and the description of one by these authors have increased the total number of reports of this type of neoplasm to 8. According to Bailey and Cushing, the tumor cells of the neuroepithelioma are primitive spongioblasts. Rosettes of cells with central canals, forming tubules or cysts, are distinctive structures of the tumor. A cuticular membrane along the lumen edge of the cells has blepharoplasten granules, and sometimes this margin has cilia. A fiber process extends from the base of each cell into the surrounding tissue. Other portions of the tumor have less definitely grouped polygonal cells and show vascular papillary stalks covered by palisades of cells which suggest the structure of tumors arising from ependymal tissues. Glia fibers are present.

A boy aged 9 years had symptoms of a tumor of the brain for seven weeks before death. A neuroepithelioma 5 by 4 by 4 cm. was found in the midline of the cerebellum, in the region of the posterior velum. It extended into both lateral recesses of the fourth ventricle.

The complete report has been published (*Zentralbl. f. allg. Path. u. path. Anat.* **69**:113, 1938).

Book Reviews

The Postmortem Examination. By Sidney Farber, M.D., Associate in Pathology, Harvard Medical School, and Pathologist to the Infant's Hospital and the Children's Hospital, Boston. Pages 201, with 33 illustrations. Price, $3.50. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

The book is divided into twelve chapters and three appendixes. Readers with a historical bent of mind will be pleased to find fifteen pages of this relatively small book given to an interesting historical introduction, which concludes with a modification of Chiari's statement on the duties of the pathologist: "The pathologist of today must be proficient in the various divisions of anatomy and embryology; he must dedicate years of activity to the routine laboratory in the acquisition of an adequate knowledge of pathologic anatomy; he must recognize problems at the autopsy and investigate them or cause them to be investigated by bacteriologic, physiologic, or chemical means; he must act as guide and as consultant to the clinicians in the solution of their routine problems; he must maintain a broad view over the whole of medicine and keep close connection with progress in the basic sciences and in the clinical fields; he must incorporate into his work new methods developed in other disciplines, and collaborate with the specialist in related lines of endeavor when a combined attack is indicated; he must fulfill the final obligation of spreading by spoken and written word what he has learned through the privilege of his position. First and last, his contributions to the field of pathology must be based upon sound training in the postmortem room. If he is to remain a fruitful worker in his field, he must not stray too far from the source that yields him both his knowledge and his problems."

In the second chapter are discussed: terminology, the difficulties connected with the obtaining of permissions for postmortem examinations, the purpose of the autopsy, the signs of death and the postmortem changes.

A quotation from an author of the sixteenth century is worth repeating here, because it lends itself for an inscription on the walls of autopsy rooms and no less appropriately on the walls of staff rooms. "Let those who interdict the opening of bodies well understand their errors. When the cause of a disease is obscure, in opposing the dissection of a corpse which must soon become the food of worms, they do no good to the inanimate mass and they cause a grave damage to the rest of mankind; for they prevent the physician from acquiring a knowledge which may afford the means of a great relief eventually to individuals attacked by a similar disease. No less blame is applicable to those physicians who, from laziness or repugnance, love better to remain in the darkness of ignorance than to scrutinize laboriously the truth, not reflecting that by such conduct they render themselves culpable toward God, themselves and society at large.—DONATUS, 1586."

Details of the equipment of the autopsy room, a list of instruments and recommendations for their care are given in chapter 3. The next chapter deals with very commendable general rules to be followed during the performance of autopsies, with recommendations for proper clothing, for care of the hands, and the handling of infections, with technical rules and with procedures for bacteriologic cultures. A list of fifty items with all the procedures that enter into the performance of an autopsy concludes the chapter. This list should help those who are less experienced to avoid serious omissions.

The following chapters are devoted to the external examination, to the primary incision, to the examination of the abdominal and thoracic cavities and to the removal of the viscera. In many instances several methods are given for a procedure and their relative advantages presented. This offers to the pathologist a choice of technic to suit the particular circumstances of the autopsy. Examination of the skull, the removal and examination of the brain and spinal cord and examination of the viscera are the subjects of the next chapters.

Autopsy technics for special cases are handled in chapter 10. They include the method of Windholz for a comparison of anatomic and roentgenologic findings, the method of LeCount and the technics for the restricted postmortem examination, the postmortem examination in the private home and the medicolegal postmortem examination. The restoration of the body and detailed, very valuable recommendations for a good protocol and for the conduct of a clinical-pathologic conference are considered briefly but very adequately. How autopsies are utilized for the instruction of students at the Harvard University Medical School is related at the close of chapter 11.

The last chapter of fifteen pages deals with the special technic of autopsies on infants and children. There is more valuable information in this chapter than in some of the much larger texts on the subject.

Appendix A consists of tables of weight of organs, Appendix B contains the copy of the report on necropsies prepared by the joint committee representing the New York Academy of Medicine, the New York Pathological Society and the Metropolitan Funeral Directors' Association. It could be used as a guide for similar committees in other cities. Appendix C is a translation of an autopsy protocol by Virchow.

Well chosen references are added at the end of each chapter.

The text is illustrated with thirty-two schematic drawings and with a frontispiece photograph of the autopsy room of the Boston Children's Hospital. The drawings are simple but instructive and convincing.

There are no words wasted in this book. The amount of information is amazingly large considering the small size. The student, the intern and the young resident and assistant will find in this book all essential data to guide them during the early stages of their career. The style is pleasing and clear. The appearance of the book, the print and the binding are excellent. The book can be recommended warmly to those who teach and to those who wish to learn pathology. It will help both.

Cutaneous Cancer and Precancer. A Practical Monograph. By George M. Mackee, M.D., Professor of Clinical Dermatology and Syphilology and Director of the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University, and Anthony C. Cipollaro, M.D., Associate in Dermatology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. Foreword by Francis Carter Wood, M.D. Cloth. Pp. 222, with 232 illustrations. Price, $3.75. New York: American Journal of Cancer, 1937.

This book is divided into four parts. The first part is a brief review of the statistical aspects of superficial cancer. Approximately 6 per cent of the deaths from cancer in the United States are due to cancer of the skin and mouth. It appears that the mortality from cancer in these locations is showing a "definite downward trend." The second part deals with the cutaneous conditions which may be followed by cancer, even if only occasionally. Some twenty forms of precancerous dermatoses are described and abundantly illustrated—a large field for the prevention of cancer. The third part takes up the malignant tumors of the skin—basal cell and squamous cell carcinoma, Paget's disease, Bowen's disease, malignant melanoma and sarcoma. The clinical, gross and microscopic descriptions and illustrations are excellent. In accord with the usage of dermatologists, carcinoma is in most cases called epithelioma. In the fourth part are discussed the general principles of the established methods of treatment of superficial cancer, mainly, of course, irradiation and operation. There is a list of references at the end of each part. The style is clear and direct. The text is illustrated lavishly with good photographs of gross and microscopic appearances. The title page states that there are 245 illustrations, but the actual number seems to be 232. The book offers a thoroughly competent discussion of skin cancer and "precancer" of marked practical value. For the pathologist it will be of great help in microscopic diagnosis.

Books Received

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEAR 1936-1937. Committee of the Privy Council for Medical Research. Paper. Price, 3 shillings. Pp. 195. London: His Majesty's Stationery Office, 1938.

PNEUMONIA AND SERUM THERAPY. Frederick T. Lord, M.D., Clinical Professor of Medicine, Emeritus, Harvard University Medical School; Member of the Board of Consultation, Massachusetts General Hospital; Member of the Massachusetts Advisory Committee on Pneumonia, 1931-1935. Roderick Heffron, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health, 1931-1935. Revised edition of Lobar Pneumonia and Serum Therapy. Cloth. Price, $1. Pp. 148, with 11 figures. New York: The Commonwealth Fund, 1938.

A TEXT-BOOK OF PATHOLOGY: AN INTRODUCTION TO MEDICINE. William Boyd, M.D., Professor of Pathology and Bacteriology, University of Toronto. Cloth. Third edition, enlarged and revised. Price, $10. Pp. 1064, with 475 illustrations. Philadelphia: Lea & Febiger, 1938.

TUBERCULOSIS AMONG CHILDREN AND YOUNG ADULTS. J. Arthur Myers, Chief of Medical Staff and Director of Tuberculosis Activities, Lymanhurst Health Center; Professor of Preventive Medicine, University of Minnesota. Second edition. Cloth. Price, $4.50. Pp. 401, with 71 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1938.

THE INFLUENCE OF X-RADIATION ON THE DEVELOPMENT OF IMMUNITY TO HETEROLOGOUS TRANSPLANTATION OF TUMORS. Johannes Clemmesen. Price, 10 kroner. Pp. 160. London: Humphrey Milford, 1938.

THE CHEMISTRY OF ANTIGENS AND ANTIBODIES. J. R. Marrack. Medical Research Council, Special Report Series, no. 230. Paper. Price, 3 shillings. Pp. 194. London: His Majesty's Stationery Office, 1938.

THE CHEMISTRY OF THE STERIDS. Harry Sobotka, Ph.D., Chemist to Mount Sinai Hospital, New York City. Cloth. Price, $8.50. Pp. 616, with 56 illustrations. Baltimore: William Wood & Company, 1938.

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